DOCKET No.: CP247 (CEPF-0006) **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: Olivier NECKEBROCK, et al.

U.S. Serial No.: 10/539,918 **Group Art Unit:** not yet known

International Application No.: PCT/FR2003/003799 **Examiner:** not yet assigned

International Filing Date: 18 December 2003

For: PROCESS FOR THE PREPARATION OF AND CRYSTALLINE FORMS OF OPTICAL ENANTIOMERS OF MODAFINIL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ERWIN BLOMSMA, PH.D.

I, Erwin Blomsma, Ph.D. hereby declare the following:

(1) I, Erwin Blomsma, Ph.D. received a Master in Engineering in Chemistry and Biochemistry in 1991, and my Ph.D. in Applied Biological Sciences in 1995 from Katholieke Universiteit Leuven, Belgium. I presently serve in a consulting capacity as Strategic Development Officer for Avantium Technologies, Zekeringstraat 29, 1014BV, Amsterdam, The Netherlands. From 2000 to 2005, I served as Vice President of Technology for Crystallics B.V. and Avantium Life Sciences, and later as COO of Avantium Technologies. The experiments discussed below were performed under my direction and control. A copy of my resume is attached hereto as Exhibit 1.

(2) MODAFINIL is the active ingredient in a commercial pharmaceutical product made by Cephalon Inc. (PA, USA). It exists in (-) and (+) isomeric forms and as a racemic mixture.

(3) In 2003, at Cephalon's request, we performed high-throughput screening for MODAFINIL polymorphs under a variety of different crystallization conditions. As part of this work, we performed recrystallizations of the (-) enantiomer from ethanol, followed by high-throughput X-ray powder diffraction (XRPD) analysis and classification of the crystalline forms produced. The methods used to perform these experiments are reported in Exhibit 2.

(4) The results of the our ethanol recrystallizations are reported in the table attached hereto as Exhibit 3. Three distinct polymorphic forms of (-)-MODAFINIL, which we designated as Form A (-)-MODAFINIL, Form B (-)-MODAFINIL and Form C (-)-MODAFINIL, were obtained from the recrystallizations from ethanol that we performed. In one instance, a mixture of Form A and Form C was obtained. In other instances, the scattering intensity of the product was too low to identify what solid form was produced (designated "n" in Exhibit 3). The XRPD patterns and DSC thermograms of Form A (-)-MODAFINIL and Form B (-)-MODAFINIL Form C (-)-MODAFINIL are shown in Exhibit 4.

(5) On the basis of the results obtained in these experiments, I conclude that recrystallization of (-)-MODAFINIL under varying conditions from ethanol can result in production of more than one crystalline form of the compound. In my experience, and based upon the data herein, recrystallization from ethanol can result in three different polymorphic forms, or a mixture of polymorphic forms, depending upon the conditions under which the recrystallization is performed.

(6) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 1st 2006

Erwin Blomsma, Ph.D.

EXHIBIT 1

Erwin Blomsma
Karrestraat 88, 3020 Herent, Belgium - T/F +32 16 201368 - Mobile +32 473 673550

Date of birth: February 29th, 1968
Nationality: Dutch

WORK EXPERIENCE

2005- present **Avantium Technologies, *Strategic Development Officer***

Leading and directing Asian business development and operations.

Strategic advisor to Avantium management team.

Analysis and commercialization of Avantium IP.

Working as consultant through own company registered in Belgium. Advisor to other companies (Carver Europe, Mettler Toledo).

2004- 2005 **Avantium Technologies, *Chief Operating Officer***

Member of the executive management team of Avantium Technologies, a contract research company specialised in rational approaches to high-throughput experimentation.

Leading and directing operations of all R&D teams in chemicals & life sciences.

2000-2004 **Avantium Technologies, *Vice President Technology***

VP Technology of Crystallics and Avantium Life Sciences. Member of the management team of Avantium Technologies. Co-founder of Crystallics.

Active role in technology development, project management and scientific collaborations.

Invited speaker and sponsor of several conferences and symposia in the domain of solid-state research and chemical & process development.

1996-2000 **Janssen Pharmaceutica NV (Johnson & Johnson),**
Manager Chemical Process Technology

Manager of the chemical process technology group and member of the international engineering management team.

Responsible for the identification, selection and implementation of new process technologies for the worldwide chemical production facilities of Janssen Pharmaceutica (Johnson & Johnson). Focus on process analytical techniques for process monitoring and control (e.g. implementation of FTIR technology for end-point detection in catalytic hydrogenation reactions, implementation of FBRM technology for in-situ particle size analysis, etc).

Played a leading role in defining and setting up a company wide knowledge management and communication system based on Lotus Notes in which proprietary and commercial knowledge bases were later integrated.

Successfully launched an ambitious project to manage the lifecycle of a pharmaceutical process from process development through scale-up and engineering to process validation in the production facilities using knowledge management and simulation tools.

EDUCATION

1995-1996 **KU Leuven / UCB Fine Chemicals,** ***Post Doctoral*** **Belgium**

Short but successful post-doctoral study on the catalytic synthesis (objective to convert a batch process to operate in continuous mode) of amine derivatives for UCB Chemicals, Belgium.

1991-1995 **KU Leuven / Shell Research KSLA,**
PhD in Applied Biological Sciences (*) **Belgium/Netherlands**

PhD thesis within the frame of a research agreement between the Shell Laboratories in Amsterdam and the centre for surface science and catalysis at Leuven University (Prof. Dr. Ir. Jacobs).

Experience was gained through the design and construction of a fully automated microreactor-setup (gas phase) including hardware and software development, data analysis and visualisation techniques.

The experimental program yielded insight in the reaction mechanisms of alkane activation and isomerization pathways and was used to design novel catalytic systems (*de novo* design). The project yielded 2 patents on bimetallic bifunctional catalysts.

(*) The centre for surface science and catalysis is part of the faculty of agricultural sciences

B

1986-1991 **KU Leuven,**
Master in Engineering in Chemistry and Biochemistry **Belgium**

Specialisation in surface chemistry and food science & technology.

Engineering thesis on the catalytic partial oxidation of methane to synthesis gas, including the design, construction and set-up of an automated reactor system with on-line GC analysis. The experimental work covered the oxidative reforming of methane, carbon dioxide and steam reforming, etc. Graduated with distinction.

OTHER EXPERIENCES AND SKILLS

Professional training:

- Process Excellence / 6 sigma (Black Belt)
- Problem solving and Decision making (Kepner Tregoe)
- Project management
- Process safety (including HAZOP, SWIFT, PHA/PHR)
- Simulation and modelling (BatchCAD, Aspen Engineering Suite, etcetera)
- Knowledge management
- Automation (DCS/PLC/Proprietary systems)
- Process analytical techniques (in situ monitoring and control)
- Process technology (unit operations: crystallisation, solid-liquid separation, drying)
- Several courses followed and workshops given on Polymorphism and crystallisation

Publications:

- 1 publication on partial oxidation of methane to synthesis gas (> 80 citations)
- 6 publications and 2 catalyst patents on "alkane hydroisomerization and hydrocracking"
- > 4 patents or patent applications in the domain of solid state research
- > 50 lectures on Solid State Research and Combinatorial Chemistry / R&D

B

EXHIBIT 2

Experimental conditions:

Approximately 7 grams of the (-) enantiomer of MODAFINIL was delivered to us in two batches as a white powder.

The crystallization experiments were carried out in stainless steel (316L) well plates. The plates contain 96 individually sealed wells of 50 μL total volume. Two of the wells in each plate utilized ethanol as the solvent. From room temperature, the plates were heated to an initial temperature of 60 or 80 °C at a rate of 4.8 °C/min and, after 30 minutes, cooled at a slow (0.6 °C/min), medium (2 °C/min) or fast (300 °C/min, maximum setting) rate to a final T of 3 °C and kept at that temperature for a minimum of 1 h or a maximum of 48 h.

After crystallization and solvent evaporation (N_2 atmosphere), the crystalline products were harvested onto a special X-ray transparent carrier. Analysis was carried out with Crystallics' T2 high throughput XRPD set-up. The plates were mounted on a Bruker GADDS diffractometer equipped with a Hi-Star area detector. The data collection was carried out at room temperature using the monochromated CuK_α radiation in the region of 2θ between 3 and 42°. The diffraction pattern for each well was collected in two 2θ ranges ($3 \leq 2\theta \leq 21°$ for the 1st frame, and $19 \leq 2\theta \leq 42°$ for the second frame) with an exposure time of between 50 and 250 seconds for each frame.

After identification of the various solid forms, thermal analysis was used for further characterization whenever enough sample was available. Melting properties were determined from differential scanning calorimetry (DSC) thermograms recorded with a DSC822e (Mettler-Toledo GmbH, Schwerzenbach, Switzerland). The DSC822e was calibrated for temperature and enthalpy with a small piece of indium (m.p. = 156.6°C; ΔH_f = 28.45 $J.g^{-1}$). Samples were sealed in standard 40 μL aluminium pans and heated in the DSC from 25 to 300°C with a heating rate of 20.0°C min^{-1}. Dry N_2 gas was used to purge the DSC equipment during measurement at a flow rate of 50 mL min^{-1}.

Mass loss due to solvent or water excretion from the crystals was determined by thermogravimetric analysis (TGA). During heating of a sample in a TGA/SDTA851e (Mettler-Toledo GmbH, Schwerzenbach, Switzerland) the weight of the sample was monitored resulting in a weight vs. temperature curve. The TGA/SDTA851e was calibrated for temperature with indium and aluminum. Samples were weighed in 70 μL alumina crucibles

and heated in the TGA from 25 to 300°C with a heating rate of 20°C min^{-1}. Dry N_2 gas was used for purging.

Digital images of the various solid forms were made using a Leica MZ9.5 stereomicroscope equipped with a Leica DC 300 digital camera.

Crystal Structure Determination

Single crystals of distinct phases identified by XRPD on the various 96-well plates were selected for full structure determination. For this, crystals were individually glued to a glass fibre, which was mounted on the X-ray diffraction goniometer. X-ray diffraction data was collected for some of these crystals at a temperature of 233 K using a KappaCCD system and Mo*K*alpha radiation generated by a FR590 X-ray generator (Bruker Nonius, Delft, The Netherlands). Unit-cell parameters and crystal structures were determined and refined using the software package maXus (Mackay *et al.*, 1997).

From the crystal structure the theoretical X-ray powder diffraction pattern was calculated using PowderCell for Windows version 2.3 (Kraus *et al.*, 1999).

Scale-Up Example:

Crystallics' Minimax parallel reactor set-up was used to conduct a series of larger scale crystallizations (in 1 mL glass vials), applying conditions selected from the polymorph screening experiments. These conditions are outlined in the results table. The Minimax reactor assembly is precision controlled and allows the precise measurement of temperature and turbidity of the crystallization solution throughout the experiment. For the experiment reported as Example 25 in Exhibit 3, 50 mg of MODAFINIL product was suspended in 333.33 µl ethanol to give a 7.5% w/v ratio. With 500 rpm continuous stirring, the crystallization mixture was heated from room temperature to 80 °C (Tmax) at 3°C/min, kept at this temperature for 30 minutes, and then cooled at 0.6 °C/min to 3 °C. The mixture was then kept at 3 °C for one hour prior to crystal structure determination.

EXHIBIT 3

Ex. No.	Heating rate (° C/min)	$T_{initial}$ (° C)	Hold (min)	Cooling rate (° C/min)	T_{final} (° C)	Hold (hour)	Modafinil Conc.	Solid Form Obtained
1	4.8	80	30	0.6	3	48	7.5%	A
2	4.8	80	30	0.6	3	48	15%	A
3	4.8	80	30	0.6	3	1	7.5%	C
4	4.8	80	30	0.6	3	1	15%	A
5	4.8	80	30	2	3	1	7.5%	A
6	4.8	80	30	2	3	1	15%	A
7	4.8	80	30	2	3	48	7.5%	A
8	4.8	80	30	2	3	48	15%	A
9	4.8	80	30	300	3	48	7.5%	B
10	4.8	80	30	300	3	48	15%	A
11	4.8	80	30	300	3	1	7.5%	A/C mixture
12	4.8	80	30	300	3	1	15%	A
13	4.8	60	30	0.6	3	48	7.5%	n
14	4.8	60	30	0.6	3	48	15%	A
15	4.8	60	30	2	3	48	7.5%	A
16	4.8	60	30	2	3	48	15%	A
17	4.8	60	30	300	3	1	7.5%	n
18	4.8	60	30	300	3	1	15%	A
19	4.8	60	30	300	3	48	7.5%	n

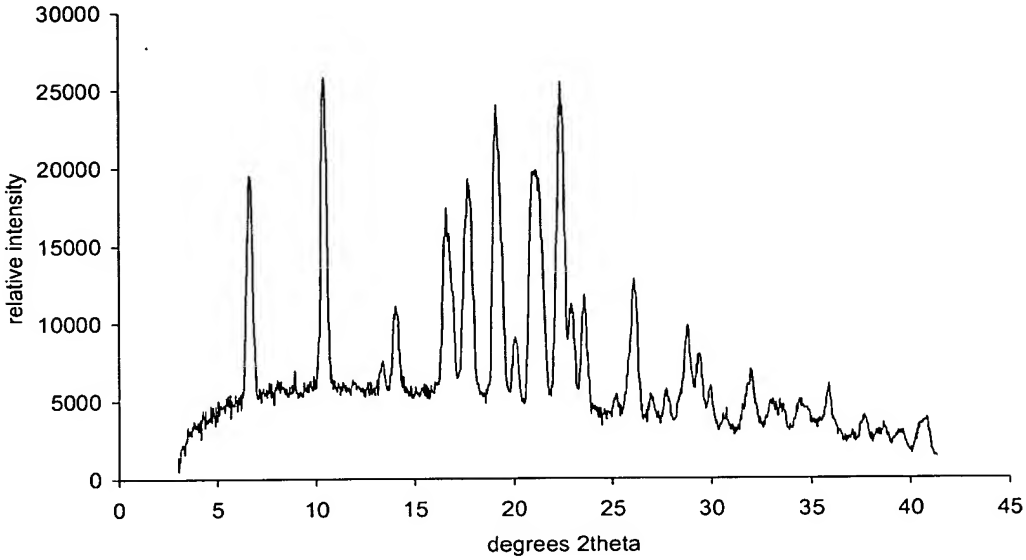
Ex. No.	Heating rate (° C/min)	$T_{initial}$ (° C)	Hold (min)	Cooling rate (° C/min)	T_{final} (° C)	Hold (hour)	Modafinil Conc.	Solid Form Obtained
20	4.8	60	30	300	3	48	15%	A
21	4.8	60	30	0.6	3	1	7.5%	n
22	4.8	60	30	0.6	3	1	15%	A
23	4.8	60	30	2	3	1	7.5%	A
24	4.8	60	30	2	3	1	15%	A
25*	4.8	80	30	0.6	3	1	7.5%	A

7.5% = 1.875 mg (-)-modafinil dissolved in 25 μl ethanol
15% = 3.75 mg (-)-modafinil dissolved in in 25 μl ethanol
Ex. No. 25* = 50 mg (-)-modafinil dissolved in 333.33 μl ethanol
n = scattering intensity of products too low to identify the solid form.

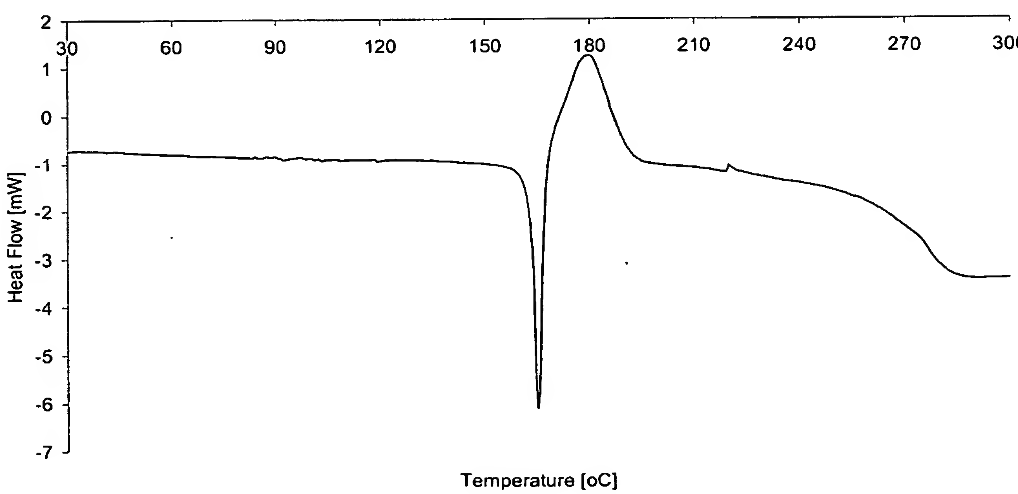
EXHIBIT 4

Crystalline Form A of (-)-MODAFINIL

XRPD

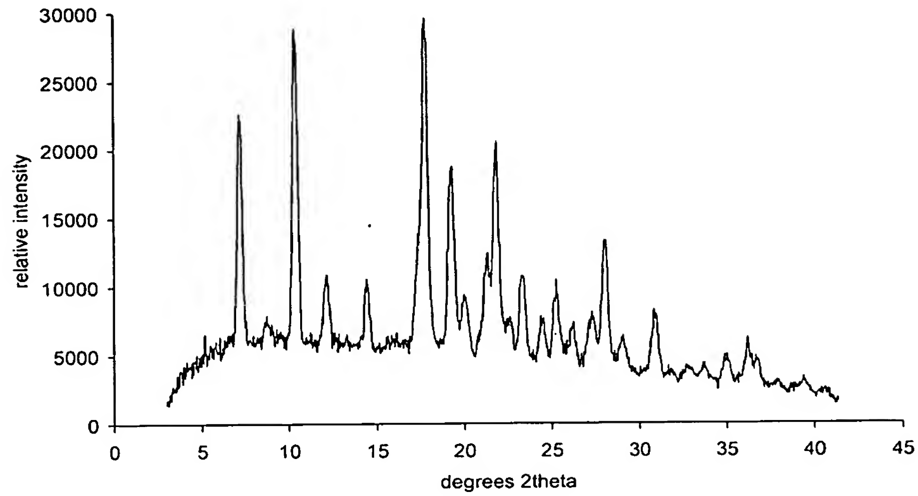


DSC

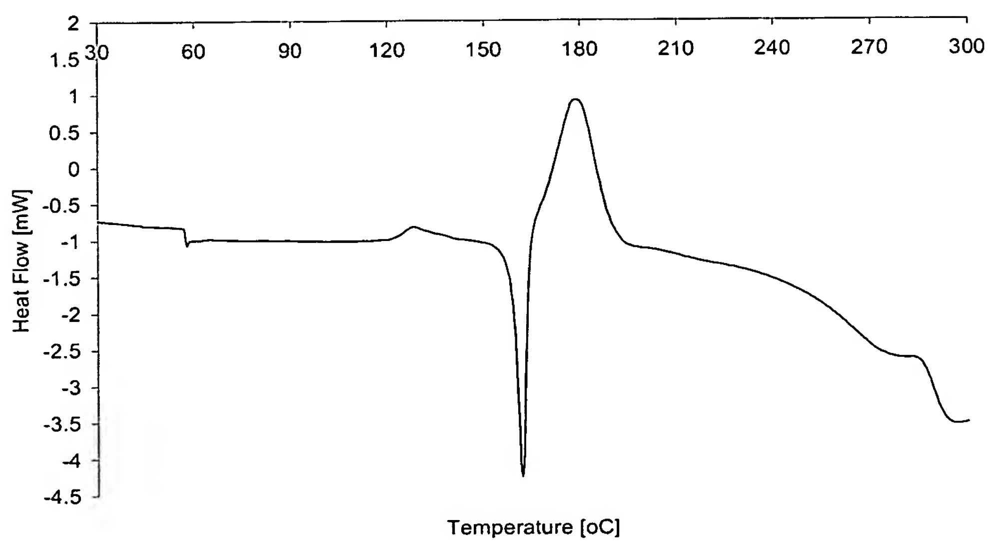


Crystalline Form B of (-)-MODAFINIL

XRPD

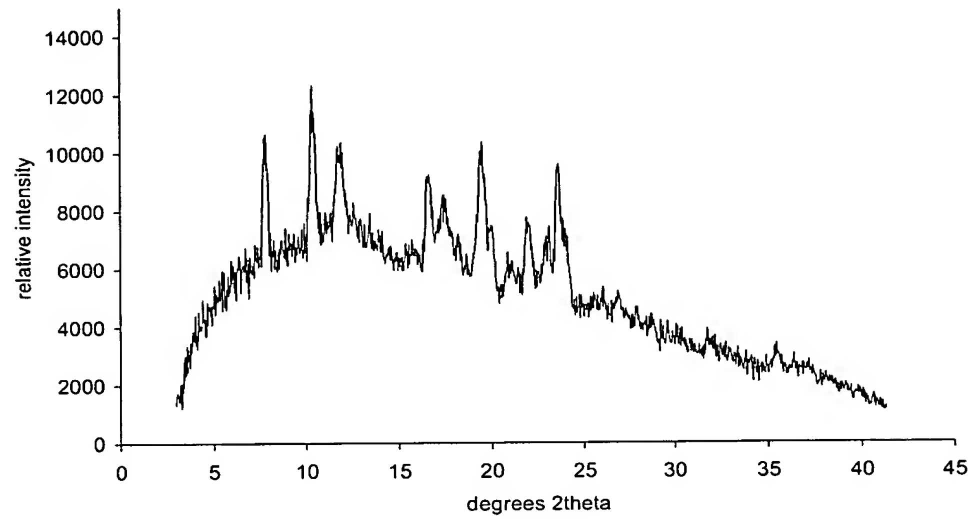


DSC

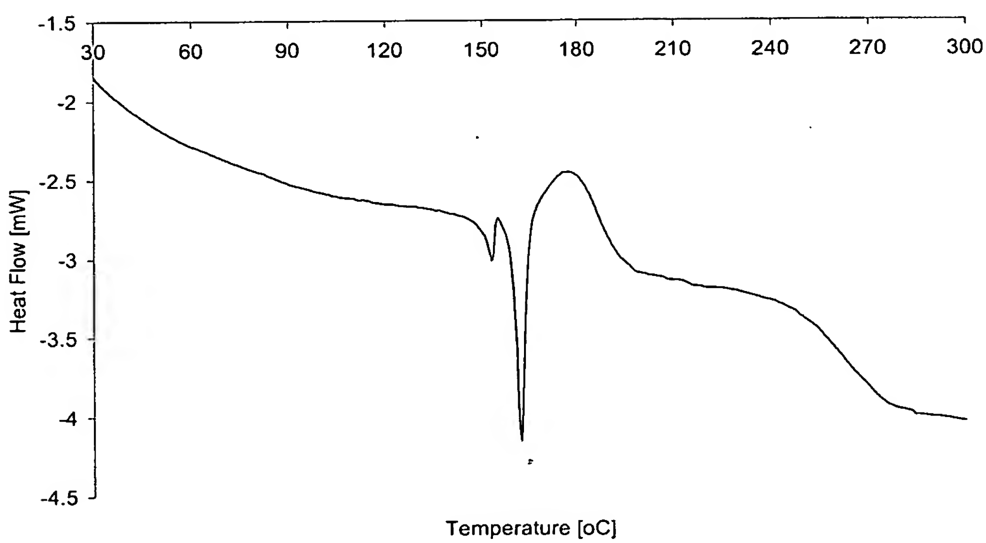


Crystalline Form C of (-)-MODAFINIL

XRPD



DSC



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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MATTHEW L. PETERSON, PHD.

I, Matthew L. Peterson, Ph.D. hereby declare the following:

(1) I received a Bachelor of Science in Chemistry from Purdue University in 1992, and a Ph.D. in Chemistry from Carnegie Mellon University in 1999. From January 2004 to the present, I have served as a Senior Scientist and Group Leader in Pharmaceutical Chemistry at TransForm Pharmaceuticals, Inc., 29 Hartwell Avenue, Lexington, MA 02421. A copy of my current *curriculum vitae* is attached hereto as Exhibit 1.

(2) MODAFINIL is the active ingredient in a commercial pharmaceutical product made by Cephalon Inc. (PA, USA). It exists in (-) and (+) isomeric forms and as a racemic mixture.

(3) TransForm Pharmaceuticals, Inc. has conducted research into various solid forms of (-)-MODAFINIL. In the process of conducting this research, we have recrystallized the (-) enantiomer of modafinil from ethanol under various conditions, as reported in paragraphs (4) to (8), *infra*. These experiments were performed under my direction and control.

(4) 29.0 mg (0.106 mmols) of (-)-MODAFINIL and 800 μl of ethanol were placed in an HPLC vial. The vial was crimp sealed, the sample was heated with a heat gun until the solids dissolved, and the septum was punctured with a needle. The sample was allowed to stand at room temperature overnight. No solids were observed in the morning. The solvent

was evaporated and the resulting solids were analyzed by powder X-ray diffraction (PXRD) and found to be the polymorph we designate as Form E (-)-MODAFINIL. A PXRD pattern of Form E of the (-) enantiomer of MODAFINIL is attached hereto as Exhibit 2.

(5) 30.1 mg (0.110 mmol) of (-)-MODAFINIL and 200 µl of ethanol were heated to 75°C and held there. After about 30 minutes some of the solids remained undissolved. An additional 200 µl of ethanol was added, and the mixture again heated to 75° C and held there. The sample was nearly dissolved. The sample was held for about another 2 hours, then cooled to 5°C at a rate of about 1°C/minute. The sample was held at 5°C for about 90 minutes, then removed from the cooling station and allowed to stand at room temperature for about 30 minutes. The sample was then dried under nitrogen and analyzed by PXRD. The sample was found to be the polymorph we designate as Form E (-)-MODAFINIL.

(6) 105.9 mg (0.3874 mmol) of (-)-MODAFINIL was slurried in 1.5 ml of ethanol. The sample was allowed to stir over the weekend at room temperature. 400 µl of the slurry was removed from the vial and centrifuge filtered. The filter cake was removed from the vial, analyzed by PXRD, and found to be the polymorph we designate as Form E (-)-MODAFINIL. Another 600 µl of the slurry was removed from the vial and centrifuge filtered. This filtrate was dried under flowing nitrogen gas. The resulting solids were analyzed by PXRD and found to be the polymorph we designate as Form D (-)-MODAFINIL. A PXRD pattern of Form D of the (-) enantiomer of MODAFINIL is attached hereto as Exhibit 3.

(7) 449.2 mg (1.643 mmols) (-)-MODAFINIL and 20.2 mg (0.074 mmols) racemic modafinil were dissolved in 5.0 ml of methanol and aliquoted into 5 vials, at 1.0 ml/vial. The methanol was allowed to evaporated, leaving behind a solid material containing (-)-MODAFINIL of about 98% purity. About 3 ml of ethanol was added to one of the vials. The sample was warmed to dissolve the material and cooled to room temperature. No solids were observed. The sample was cooled to 0°C, where solids were observed. The solids were isolated by filtration and dried. The sample was left overnight. The next day, the sample was analyzed by PXRD and found to be the polymorph we designate as Form D (-)-MODAFINIL.

(8) About 70 mg para-toluenesulfonic acid monohydrate was added to a solution of 15.8 grams (-)-benzhydrylsulfinylacetic acid in 150 ml methanol. The reaction was stirred

at reflux for two hours, cooled to room temperature, and stirred overnight at room temperature to produce a solution of (-)-benzhydrylsulfinyl methyl ester. 75 ml of this solution was taken up and transferred to a 3-necked round bottom flask equipped with a condenser and a magnetic stir bar. 50 ml of methanol were added, and anhydrous ammonia was bubbled through the reaction mixture for 10 minutes. A precipitate began to form, and was collected using a Hirsh funnel to give a solid (422 mg) which was characterized by NMR as a side product. The filtrate was then acidified using HCl and concentrated under vacuum to give a solid with was purified using column chromatography, using 3:1 mixture of ethyl acetate:hexane as the eluant. The filtrates from the column were then combined and concentrated *in vacuo* to (-)-MODAFINIL as a colorless solid (590 mg). PXRD analysis was performed on this solid, and it was determined to be the polymorph we designate as Form D (-)-MODAFINIL. This solid was then dissolved in about 3 ml ethanol by heating to boiling with a heat gun. The sample was allowed to cool on the bench top. Crystallization was observed at room temperature. The crystals were isolated by filtration on a Büchner funnel and allowed to air dry on the filter. The crystals were characterized by PXRD and found to be the polymorph we designate as Form E (-)-MODAFINIL.

(9) Based on the experiments described in paragraphs 4 to 8, *supra*, I conclude that recrystallization of (-)-MODAFINIL from ethanol under varying conditions may result in formation of more than one polymorph form of the compound. In my experience, and based on the data herein, different polymorphic forms of the compound may be produced, depending upon the conditions under which the recrystallization is performed.

(10) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 01-June-2006

Matthew L. Peterson, Ph.D.

EXHIBIT 1

Matthew Lynn Peterson

TransForm Pharmaceuticals, Inc.
29 Hartwell Avenue
Lexington, MA 02421
(781) 674-7822
mpeterson@transformpharma.com

25 Downey Street
Hopkinton, MA 01748
(508) 625-1307
mp5y_cmu@yahoo.com

Experience

TransForm Pharmaceuticals, Inc.

Senior Scientist – Group Leader, Pharmaceutical Chemistry (January 2004 – present)
Managed a group of 6 people including 3 Ph. D., 1 M. S. and 2 B. S. level scientists. Interfaced with engineering and software development groups to develop an automated crystallization platform that was deployed to several off-site research groups. Interfaced with discovery groups on lead optimization focusing on the importance of physical properties of the compounds being advanced. Lead project teams through form evaluation and characterization, excipient compatibility, formulation design, crystallization scale up and in vitro and in vivo testing. Headed and expanded a research collaboration with the University of South Florida focused on pharmaceutical co-crystals and solvent sparing synthetic methods. Continued to lead the internal publications efforts. Member of Science and Technology Organization and Research Management team.

Senior Scientist in Pharmaceutical Research (January 2003 – January 2004)
Identified and carried out physico-chemical evaluation of several compounds for internal drug development program. Evaluated the pharmacokinetic and pharmacodynamic performance of development compounds using animal studies. As part of a product research program formulated strategy for development and/or outsourcing of new drug candidates. Headed research collaboration with an academic research group at The University of South Florida focused on the development of new methods for the modification of the physical performance of pharmaceutical compounds by modification of their solid form. Managed several interns, one MS level assistant scientist and one Ph. D. level scientist. Lead internal publication efforts. Provided training for proper laboratory notebook practices to new scientific staff. Sourced compounds for exploratory studies for internal drug development efforts.

Scientist in Solid State Chemistry and Targeted Discovery (August 2001 – January 2003)
Studied polymorphism, hydrates, solvates and salts of pharmaceutical compounds using traditional high-throughput crystallization techniques. Developed novel process upgrades to TransForm's high-throughput crystallization platform. Developed crystallization screen focused on inhibition of calcium oxalate crystal growth. Supervised multidisciplinary team responsible for development of automated experimentation platforms. Managed outsourcing of single crystal X-ray structure determination. Acted as the contact person and led internal scientific efforts for several projects with outside partners. Managed several interns, one MS level assistant scientist and one Ph. D. level scientist. Lead internal publication efforts. Provided training for proper laboratory notebook practices to new scientific staff. Sourced compounds for exploratory studies for internal drug development efforts.

Kansas State University, Manhattan, KS (October 1999 – August 2001).
Postdoctoral research with Prof. Mark D. Hollingsworth
Studying the ferroelastic and ferroelectric properties of urea and thiourea inclusion crystals and 4-tert-butlycalix[4]arene clatharates. Synthesized and characterized organic, organometallic and isotopically labeled compounds. Determined the single crystal structures of these often disordered and/or twinned crystals using X-ray diffraction techniques. Optimized crystal growth

conditions to yield centimeter sized crystals for X-ray topography. Installed and maintained a 300 MHz NMR used for solid state magic angle spinning experiments. Assisted in the design of novel instrumentation used to study ferroelasticity and ferroelectricity at high and low temperatures by optical microscopy.

Carnegie Mellon University, Pittsburgh, PA (July, 1993 – October, 1999)
Ph. D. with Prof. Stuart W. Staley
Focused on molecular structure and dynamic molecular processes in the solid and liquid state. Synthesized and characterized the compounds utilized in these studies. Measured dynamic molecular process using NMR methods, including full line shape analysis and saturation transfer. Determined single crystal structures using X-ray diffraction techniques. Maintained, administered and upgraded the group's GE 300 MHz NMR. Organized departmental graduate student seminar series. Departmental teaching assistant of the year, 1996. Teaching assistant 1993 - 1999.

University of Umeå, Umeå, Sweden (July-Aug. 1997; June-July 1998)
Research assistant, advisor: Professor Bertil Eliasson
Part of a collaborative research program involving the determination of rate constants for the dynamic processes of bridged dicyclooctatetraenes and their dianionic salts by dynamic NMR spectroscopy. Worked with a Bruker 360 MHz NMR spectrometer.

Purdue Univeristy, West Lafayette, IN (December, 1991 – June, 1993)
Undergraduate research with Prof. Bart Kahr
Grew and optically characterized mixed crystals of sodium chlorate / sodium bromate and lead nitrate / barium nitrate. Grew organic dye inclusion crystals (inorganic crystals with organic dye inclusions). Organized and maintained a crystal library.

Education
Carnegie Mellon University, Pittsburgh, PA
Ph. D. Chemistry October, 1999

Purdue University, West Lafayette, IN
B.S. Chemistry December, 1992

Instrumentation and Computer Programs

Single crystal and powder x-ray diffraction, Raman Spectroscopy, ^{1}H and ^{13}C variable temperature NMR, Spin-Saturation Transfer (SST), IR, UV-VIS, polarized light microscopy, thermal microscopy, analytical and preparative HPLC, GC, DSC, TGA. TGA-IR, ultrafast video microscopy, Synchrotron White Beam X-ray Topography, NLO microscopy, CP/MAS NMR, GC/mass spectroscopy,. Gaussian92, Gaussian94W, Gaussian98W and Gaussian03W, the Cambridge Structural Database, Materials Studio and Cerius2 packages of programs, Shelx, SMART, SAINT, CrystalStructure and Sir93 crystals structure determination and refinement software, gNMR, Microsoft Word, Excel, PowerPoint, Outlook, Adobe Photoshop and Premier.

Experimental Techniques

High-throughput combinatorial crystallization. High-throughput chemical library screening. Experienced in multi-step and microscale synthesis of organic compounds utilizing anhydrous, oxygen free and low temperature techniques. Practiced in dynamic, 1D and 2D NMR techniques used for characterization of organic compounds and determination of rate constants of dynamic molecular processes. Determination of single crystal x-ray structures by direct methods using both serial and area detectors. Optimization of molecular structures, calculation of energy barriers and electron distributions using semi-empirical, molecular mechanics and *ab initio*

methods. Controlled crystal growth and habit modification. Synchrotron Whitebeam X-ray Topography. Single crystal ferroelastic and ferroelectric experiments.

Patents

Topiramate Salts and Compositions Comprising and methods of making and using the same. 10/637,829, filed 8/8/2003.
Topiramate Sodium Trihydrate. PCT/US03/04357 filed 2/14/2002.
Topiramate Salts and Compositions Comprising them. 10/295,995 filed 11/28/2002.
Novel Conazole Crystalline Forms and Related Processes, pharmaceutical Compostions and Methods. 10/449,307 filed 5/30/2003.
High-Throughput Methods of forming, identifying and analyzing solid-forms, and their use to obtain polymorphs of acetaminophen. 60/377,211 filed 5/3/2002.
High Throughput methods and systems for screening of compound to treat/prevent kidney disorders. PCT/US03/17574 filed 6/4/2003
Pharmaceutical Compositions with Improved Dissolution. 10/601,092 filed 6/20/2003.
Pharmaceutical Compositions with Improved Solubility. PCT/US03/19574 filed 6/20/2003.
Crystalline Salts of Celecoxib. 11/25/2003.
Pharmaceutical Co-crystal Composition. 60/451,213 filed 2/28/2003.
Pharmaceutical Compositions. 60/487,064 filed 7/11/2003
Gabentin Compositions. 60/462,179 filed 4/11/2003
Sertaline Compositions. 60/472,939 filed 5/23/2003
Sertraline Compositions. 60/492,141 filed 8/1/2003
Sertaline Compositions. 60/492,868 filed 8/6/2003
Mixed co-crystals and pharmaceutical compositions. US 2005267209, 53 pp.
Preparation of organic acid salts of gabapentin. WO 2004091278

Publications

Vishweshwar, Peddy; McMahon, Jennifer A.; Oliveira, Mark; Peterson, Matthew L.; Zaworotko, Michael J. The Predictably Elusive Form II of Aspirin. J. of the Am. Chem. Soc. **2005**, 127(48), 16802-16803.

Hollingsworth, Mark D.; Peterson, Matthew L.; Rush, Jeremy R.; Brown, Michael E.; Abel, Mark J.; Black, Alexis A.; Dudley, Michael; Raghothamachar, Balaji; Werner-Zwanziger, Ulrike; Still, Ezra J.; Vanecko, John A. Memory and Perfection in Ferroelastic Inclusion Compounds. Crystal Growth & Design **2005**, 5(6), 2100-2116.

Vishweshwar, Peddy; McMahon, Jennifer A.; Peterson, Matthew L.; Hickey, Magali B.; Shattock, Tanise R.; Zaworotko, Michael J. Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients. Chem Commun (Cambridge, United Kingdom) **2005**, (36), 4601-4603.

Hollingsworth, Mark D.; Peterson, Matthew L.. Twinning, epitaxy and domain switching in ferroelastic inclusion compounds. NASA Conference Publication **2003**), 2003-212339(2002 Microgravity Materials Science Conference), 283-288.

High-Throughput Survey of Crystal Form Diversity of Highly Polymorphic Pharmaceutical Compounds Örn Almarsson, Magali B. Hickey, Matthew L. Peterson, Sherry L. Morissette, Stephen Soukasene, Chris McNulty, Mark Tawa, J. Michael MacPhee and Julius F. Remenar, *Crys.l Growth Des.n*, **2003**, Vol. 3, No. 5.

Crystallization and Transformation of Acetaminophen Trihydrate Matthew L. Peterson, David McIlroy, Paul Shaw, J. Peter Mustonen, Mark Oliveira and Örn Almarsson, *Cryst, Growth Des.*, **2003**, *3(5)*, 761-765.

Crystal Engineering of Novel Co-Crystals of a Triazole Drug with 1,4-Dicarboxylic Acids, Julius F. Remenar, Sherry L. Morissette, Matthew L. Peterson, Brian Moulton, J. Michael MacPhee, Héctor Guzmán, Örn Almarsson, *J. Am. Chem. Soc.*, **2003**, *125(28)*, pages 8456-8457.

Quinoline Binding Site on Malaria Pigment Crystal: A Rational Pathway for Antimalaria Drug Design Buller, R.; Peterson, M. L.; Almarsson, O.; Leiserowitz, L. *Cryst. Growth Des.* **2002**; *2(6)*, 553-562.

Iterative High-Throughput Polymorphism Studies on Acetaminophen and an Experimentally Derived Structure for Form III Peterson, M. L.; Morissette, S. L.; McNulty, C.; Goldsweig, A.; Shaw, P.; LeQuesne, M.; Monagle, J.; Encina, N.; Marchionna, J.; Johnson, A.; Gonzalez-Zugasti, J.; Lemmo, A. V.; Ellis, S. J.; Cima, M. J.; Almarsson, O. *J. Am. Chem. Soc.* **2002**; *124(37)*, 10958-10959

Unanticipated Guest Motion during a Phase Transition in a Ferroelastic Inclusion Compound Hollingsworth, M. D.; Peterson, M. L.; Pate, K. L.; Dinkelmeyer, B. D.; Brown, M. E. *J. Am. Chem. Soc.* **2002**, *124(10)*, 2094-2095.

Relationship Between Molecular Structure, Polarization and Crystal Packing in 6-Arylfulvenes.Staley, Stuart W.; Peterson, Matthew Lynn and Wingert, Lavinia M. R. Glaser, P. Kaszynski, Eds. *ACS Symposium Series, Volume 798.* American Chemical Society: Washington, D.C., **2001**.

Grafting Copolymers of Polyethylene by Atom Transfer Radical Polymerization. Matyjaszewski, K.; Teodorescu, M.; Miller, P. J.; Peterson, M. L. *J. Polym. Sci. A: Polym. Chem.* **2000**, *38*, 2440-2448.

Structural Effects of C6 Substitution in 6-(4-(Dimethylamino)phenyl)fulvenes. Peterson, Matthew L.; Strnad, Jeffrey T.; Markotan, Thomas P.; Morales, Carl A.; Scaltrito, Donald V.; Staley, Stuart W. *J. Org. Chem.* **1999**, *64(25)*, 9067-9076.

Grafting styrene and acrylates from functionalized polyethylene by atom transfer radical polymerization. Miller, Peter J.; Teodorescu, Mircea; Peterson, Matthew L.; Matyjaszewski, Krzysztof *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1999**, *40(2)*, 426-427.

Crystal and Molecular Structures of (*E*)-2-Phenylethenyl)cyclooctatetraene and (*E*)-(2-(4-Nitrophenyl)ethenyl)cyclooctatetraene. Conformations of Substituted Cyclooctatetraenes. Peterson, Matthew L.; Staley, Stuart W. *Structural Chemistry* **1998**, *9(4)*, 305.

Effects of Habit Modification on Optical and X-ray Structures of Sodium Halite Mixed Crystals: The Etiology of Anomalous Double Refraction. Crundwell, Guy; Gopalan, Prakash; Bakulin, A; Peterson, Matthew L.; Kahr, Bart *Acta Crystallogra.* **1996**, *B53*, 189.

Organic Hourglass Inclusions: A Review of Past and Recent Work and a Student Experiment. Kahr, Bart; Chow, Jason; Peterson, Matthew L. *J. Chem. Ed.* **1994**, *71(7)*, 584.

Reevaluating Structures for Mixed Crystals of Simple Isomourphous Salts: Sodium Chlorate Bromate ($NaCl_xBr_{1-x}O_3$). Gopalan, Prakash; Peterson, Matthew L.; Crundwell, Guy; Kahr, Bart *J. Am. Chem. Soc.* **1993**, *115(3)*, 3366.

Lectures and Posters

ICCOSS talk

ACA talk

High-Throughput Polymorphism Studies on Acetaminophen and an Experimental Analysis of the Metastable Form III. American Chemical Society Lecture. August, **2002**.

Tailor-Made Impurity Control of Elastic Versus Plastic Domain Switching in Ferrolastic Inclusion Compounds Poster, Gordon Conference on Organic Compounds in the Solid State, June, **2000**.

Tailor-Made Impurity Control of Elastic Versus Plastic Domain Switching in Ferrolastic Inclusion Compounds. Lecture, Midwest Solid State Organic Chemistry Conference, June, **2000**.

Structural Effects of C6 Substitution in 6-(4-(Dimethylamino)phenyl)fulvenes. Midwest Solid State Organic Chemistry Conference, **1999**.

The influence of Crystal Packing on the Electron Density and Solid State ring Flipping in 6-(4-Anisol)-6-methylfuvlene. American Chemical Society Poster, **1995**.

The Molecular and Crystal structures of a Series of 6-(4-(Dimethylamino)phenyl)fulvenes. Midwest Solid State Organic Chemistry Conference, **1995**.

Electronic Effects of *para*-Substitution on the Molecular Structures of 6-Aryl-6-methylfulvenes. American Chemical Society Lecture, **1994**.

EXHIBIT 2

PXRD of (-)-MODAFINIL Form E:

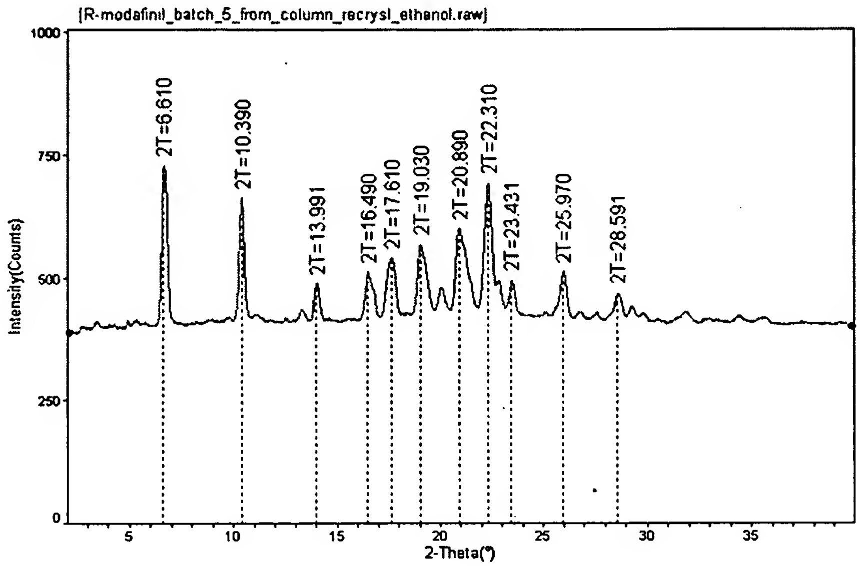
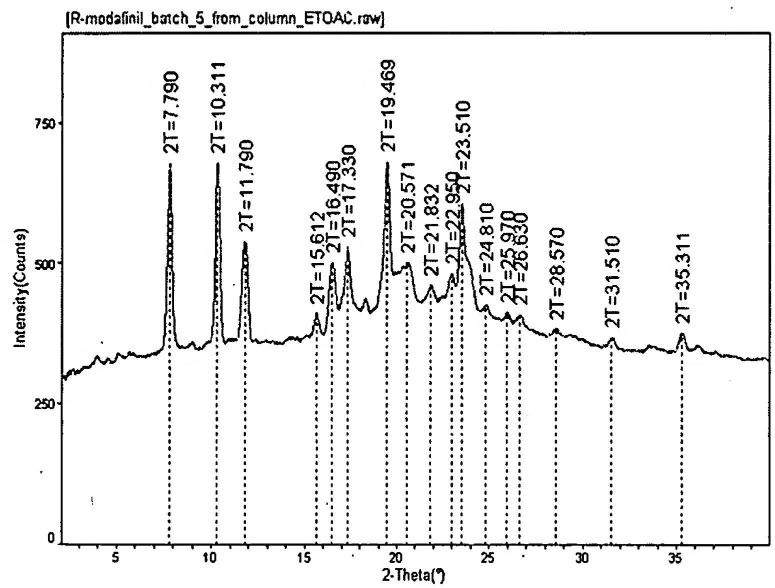


EXHIBIT 3

PXRD of (-)-MODAFINIL Form D:



DOCKET NO.: CP247 (CEPF-0006) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Olivier Neckebrock, et al.**	Confirmation No.: **8401**
Application No.: **10/539,918**	Group Art Unit: **Not yet Assigned**
Filing Date: **February 17, 2006**	Examiner: **Not Yet Assigned**

For: **Process For the Preparation of and Crystalline Forms of Optical Enantiomers of Modafinil**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JOHN P. MALLAMO, PH.D.

I, John P. Mallamo, Ph.D. hereby declare the following:

(1) I received a Bachelor of Science in Chemistry from Colorado State University in 1977, and a Ph.D. in Organic Chemistry from Johns Hopkins University in 1981. From January 2002 to the present, I have served as Vice President, World Wide Chemical Research & Development, at Cephalon, Inc. 41 Moores Road, P.O. Box 4011, Frazer, PA 19355. A copy of my current *curriculum vitae* is attached hereto as Exhibit 1.

(2) Modafinil is the active ingredient in a commercial pharmaceutical product made by Cephalon Inc. It exists in (-) and (+) isomeric forms and as a racemic mixture.

(3) I have reviewed and am familiar with the above-captioned patent application which, among other things, describes polymorphic forms of (-)-modafinil and methods of preparing same. In particular, the patent application describes a particular polymorph of (-)-modafinil that is denominated as "Form I." This polymorph is described as one that produces a powder X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings: 8.54, 4.27, 4.02 and 3.98 (Å), and a powder X-ray diffraction spectrum comprising reflections at 15.4, 31.1, 33.1 and 33.4 degrees 2θ.

(4) I have also reviewed and am familiar with Lafon, U.S. Patent No. 4,177,290 ("the Lafon '290 patent"). The Lafon '290 patent describes the preparation of

"benzhydrylsulphinylacetamide" which is an alternative chemical name for modafinil (also referred to as CRL 40476).

(5) The preparatory methods described in the Lafon '290 patent produce the modafinil racemate, not the individual (+/-) enantiomers of modafinil. Accordingly, the statement in the instant application that "l-modafinil and d-modafinil prepared according to the conditions described in US patent 4,177,290 are obtained in the form of one polymorphic form described as form I" is erroneous. The Lafon '290 patent does not teach or suggest the preparation of any specific forms of (-)-modafinil, let alone the Form I polymorph. Indeed, the Lafon '290 patent does not even indicate that racemic modafinil may exist in multiple polymorphic forms.

(6) I have also reviewed and am familiar with Lafon, U.S. Patent No. 4,927,855 ("the Lafon '855 patent"). Preparation I, at column 3, lines 5 to 57 of the Lafon '855 patent, describes the synthesis of (-)benzhydrylsulfinylacetamide, which is a chemical name for the compound known as (-)-modafinil (also referred to as CRL 40982, l-modafinil, or armodafinil). In the final step of the described synthesis, the residue is taken up in ether, the product filtered off and "recrystallized from ethanol to give CRL 40 982." At column 3, lines 53 to 55, the Lafon '855 patent indicates that the product of Preparation I is in the form of white crystals that are soluble in alcohols and acetone and insoluble in water and ether. The melting point (inst.) of the product is said to be 153° - 154°C.[1]

(7) The experiment underlying Preparation I of the Lafon '855 patent was performed at Laboratoire L. Lafon (now Cephalon France) a number of years ago. After research and investigation into their files, scientists and others at Cephalon France and Organisation De Synthese Mondaile Orsymonde have been unable to locate any remaining samples of this batch of (-)-modafinil, or any record of a powder X-Ray diffraction (PXRD) spectrum ever having been obtained on a sample of this batch. To the best of my knowledge, the product of the experiment that provides the basis of Preparation I has never been analyzed

[1] The abbreviation "inst." in the Lafon '855 patent indicates that the value given is an "instantaneous" melting point. Instantaneous melting points are obtained using a device such as a Kofler hot bar which has an electrically heated stage that is designed to have a nearly linear temperature gradient along its length. The instantaneous melting point is obtained by placing a thin layer of the sample on the hot stage along the temperature gradient, and identifying the point on the stage where melting occurs. Scientists at Cephalon France familiar with the experiment that underlies Preparation I in the '855 patent have advised that a Kofler hot bar was used to obtain the instantaneous melting point reported in Preparation I.

by PXRD or any other analytical method capable of identifying and/or distinguishing polymorphic forms of (-)-modafinil.

(8) The Lafon '855 patent nowhere teaches or suggests that (-)-modafinil may take on different polymorphic forms, or that the product of Preparation I is a polymorph, as opposed to some other crystalline form. Nor does the patent teach or suggest the specific Form I polymorph recited in the instant application. Moreover, the reference provides no information regarding the PXRD spectrum of the product. Thus, the Lafon '855 patent fails to provide any express disclosure of the Form I (-)-modafinil polymorph that is described and claimed in the present application.

(9) It is known in the art that different recrystallization conditions can have a significant impact on the solid form produced and minor variations in the conditions can lead to different polymorphic forms. The Lafon '855 patent is silent regarding the detailed conditions under which the ethanol recrystallization utilized in Preparation I was performed. The patent does not specify any particular grade of ethanol, and the concentration of the (-)-modafinil/ethanol solution used in the recrystallization is likewise not described. Moreover, no process conditions for the recrystallization are set forth. For example, the Lafon '855 patent does not indicate whether the solution was heated to dissolve the (-)-modafinil, and if so, whether it was heated to reflux. The patent also does not teach a rate at which the solution was then cooled, to what temperature, how the solvent was removed, or how the product was dried.

(10) I am aware that scientists at Cephalon France and Organisation De Synthese Mondaile Orsymonde, as part of their ongoing work with modafinil and its enantiomers, have on several occasions obtained PXRD spectra of polymorphic forms of (-)-modafinil that have been recrystallized from ethanol. Although this work was not performed under my direction and control, I have reviewed the data and reports and conferred with scientists involved with the experiments. The experimental conditions recorded by the scientists in their lab notebooks, and the polymorphic form[2] obtained from these recrystallizations, have been compiled and are set forth in the table attached hereto as Exhibit 2.

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[2] The terms Form I, Form II and Form IV used herein to designate different polymorphic forms of (-)-modafinil corresponds to the nomenclature set forth in the instant application.

(11) The recrystallizations set forth in Exhibit 2 generally entailed mixing (-)-modafinil with either absolute ethanol, denatured ethanol (*i.e.*, a mixture of 97.5% ethanol and 2.5% toluene), or either one of these grades of ethanol with 3% water added, heating to dissolve the (-)-modafinil, followed by cooling in an ice bath. The (-)-modafinil crystals were then collected by filtration, dried and analyzed sometime thereafter by PXRD.

(12) The data reported in Exhibit 2 shows that one of the recrystallizations yielded a mixture of Form I and Form IV,[3] one of the recrystallizations yielded Form II, and the remainder yielded Form I. A composite image showing the PXRD spectra obtained for Example Nos. ON II/149E, ON II/149H, ON II/150A and ON II/150B is attached hereto as Exhibit 3. It is evident from this image that the X-ray diffraction spectrum for Example No. ON II/149H (second from bottom) is different than the X-ray diffraction spectrum of the other three examples.

(13) The experiments reported in Exhibit 2 show that a different polymorph was produced when using denatured ethanol as the solvent (Example No. ON II/149H) than when using absolute ethanol as the solvent (Example No. ON II/149E). Moreover, a comparison of Example No. ON II/149H and Example No. 1/0920 show that two recrystallizations from denatured ethanol do not always yield the same polymorphic form of (-)-modafinil.

(14) The experiments reported in Exhibit 2 also show that recrystallization from absolute ethanol in one instance (Example No. 5/2502) produced Form I (-)-modafinil, but in another instance (Example No. 1/0054a) produced a mixture of Form I and Form IV.[4]

(15) In view of these experiments, it is my opinion that recrystallization of (-)-modafinil from ethanol produces more than one form of (-)-modafinil, and does not necessarily produce Form I (-)-modafinil.

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[3] When a second PXRD was performed on a sample from this batch five years later, the sample was found to be only Form I (-)-modafinil.

[4] Experiments 1/0054(a) and 1/0054(b) also show that one polymorphic form of (-)-modafinil may spontaneously convert to a more stable polymorphic form over time. Specifically, when first examined about 9 months after the recrystallization was performed, this sample was found to produce an X-ray diffraction spectrum characteristic of a mixture of Form I and Form IV (-)-modafinil. However, when examined about 5 years later, the sample was found to produce an X-ray diffraction spectrum characteristic of pure Form I (-)-modafinil. I do not consider this finding to be unexpected or surprising;, as the Applicants have stated in the present application, that Form I is the more thermodynamically stable polymorphic form of (-)-modafinil.

(16) I have reviewed and am familiar with the data reported in the Declaration of Erwin Blomsma, Ph.D., prepared for submission in the instant application. Dr. Blomsma indicates that three distinct polymorphs of (-)-modafinil were obtained from ethanol recrystallization. The polymorphic form denominated Form A by Dr. Blomsma appears to correspond to the Form I (-)-modafinil polymorph of the instant application. I agree with Dr. Blomsma's conclusions, based on that data, that recrystallization of (-)-modafinil from ethanol under varying conditions can produce more than one crystalline form of the compound.

(17) I have reviewed and am familiar with the data reported in the Declaration of Matthew Peterson, Ph.D., also prepared for submission in the instant application. Dr. Peterson indicates that two distinct polymorphs of (-)-modafinil were obtained from ethanol recrystallization. The polymorphic form denominated Form E by Dr. Blomsma appears to correspond to the Form I (-)-modafinil polymorph of the instant application. I agree with Dr. Peterson's conclusions, based on that data, that different polymorphic forms of the compound may be produced depending upon the conditions under which ethanol recrystallization is performed.

(18) The data obtained by scientists at Cephalon France and Organisation De Synthese Mondaile Orsymonde, together with the data reported in the Declaration of Erwin Blomsma, Ph.D. and the Declaration of Matthew Peterson, Ph.D., show that varying the conditions under which (-)-modafinil is recrystallized from ethanol (such as the rate of cooling, the type of ethanol utilized, the (-)-modafinil concentration, the length of time the crystals are held at the final crystallization temperature prior to analysis, and other factors) produces different polymorphic forms. On the basis of this data, I conclude that without detailed information regarding such conditions, one cannot predict with any degree of certainty what polymorphic form will be produced by recrystallization of (-)-modafinil from ethanol.

(19) Scientists at Cephalon France and Organisation De Synthese Mondaile Orsymonde have measured the instantaneous melting point of known polymorphic forms of (-)-modafinil at various times over the course of several years. Instantaneous melting points were obtained using a Kofler hot bar, described previously, which, to my knowledge and understanding, is the same instrument used to obtain the melting point of the (-)-modafinil sample produced in Preparation I of the '855 patent. The table attached hereto as Exhibit 4

presents this instantaneous melting point data.[5] The data in this table shows that measurements of the instantaneous melting point of Form I (-)-modafinil ranged between 159° - 164°C, while the instantaneous melting point of Form II (-)-modafinil was found to be 156°C. Measurements of the instantaneous melting point of Form I mixed with another polymorph (either Form II or Form IV) of (-)-modafinil ranged between 156° - 164°C.

(20) The data reported in Exhibit 4 shows that the instantaneous melting point of Form I (-)-modafinil, as measured with a Kofler hot bar, ranges between 159° - 164°C. The product of Preparation I of the '855 patent is reported to have an instantaneous melting point (also obtained using a Kofler hot bar) of 153° - 154°C, which is outside this range, and closer to the instantaneous melting point obtained for Form II (-)-modafinil.[6] While, in my opinion, one cannot conclusively determine from this data which crystalline form was produced by Preparation I of the Lafon '855 patent, since the instantaneous melting point reported in the Lafon '855 patent does not appear to correspond to the instantaneous melting point of Form I (-) modafinil, the data supports a conclusion that the (-)-modafinil described in Preparation I of the Lafon '855 patent is NOT the claimed Form I (-)-modafinil.

(21) On the basis of the melting point experiments reported in paragraphs (19) and (20), it is my considered opinion that the product obtained by Preparation I of the Lafon '855 patent was not necessarily the claimed Form I (-)-modafinil polymorph. In my opinion one cannot, based on the teaching of an instantaneous melting point of 153° - 154°C, conclude

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[5] In the interest of full disclosure, it is noted that Exhibit 4 does not include Example No. 5/2173, which involved recrystallizing (-)-modafinil from isopropanol. The product of this example was found to have an instantaneous melting point of 153° - 154°C when first prepared, but its PXRD spectrum was not taken at that time, so it is not known what polymorphic form was present when the instantaneous melting point was identified. Three years later, the sample was analyzed by PXRD, and found to produce a spectrum consistent with Form I (-)-modafinil. However, no instantaneous melting point was taken at this time. Thus, there was never a contemporaneous assessment of both instantaneous melting point and PXRD for this sample. Since it is possible that the sample may have converted to Form I (-)-modafinil during storage (see footnote 4, above), this lack of contemporaneous correlation between instantaneous melting point and PXRD spectrum renders correlation of the data for this sample unreliable. Accordingly, data relating to Example No. 5/2173 was not included in Exhibit 4.

Similarly, Example No. 1/0054(b) (shown in Exhibit 2, and discussed previously) was not included in Exhibit 4, because the only instantaneous melting point obtained for the sample (164°C) was taken some five years prior to obtaining the corresponding PXRD spectrum (shown to be Form I). The melting point of 164°C obtained for Example No. 1/0054(a) is included in Exhibit 4, however, because the melting point was obtained within several months of obtaining the corresponding PXRD spectrum (shown to be a mixture of Form I and Form IV).

[6] If one were to include the two excluded samples referenced in footnote 5, the instantaneous melting point range for Form I (-)-modafinil would range between 153° - 164°C, and overlap with the instantaneous melting point obtained for Form II (-)-modafinil (156°C). As such, one would be unable to distinguish between polymorphic forms on the basis of instantaneous melting point.

that Preparation I of the Lafon '855 patent necessarily describes the claimed Form I (-)-modafinil polymorph.[7]

(22) As noted in paragraph (8) above, based on my review of the Lafon '855 patent, I conclude that the reference does not expressly describe Form I (-)-modafinil. Moreover, as noted above, one cannot conclude from the teaching in the Lafon '855 patent that the reported crystalline form of (-)-modafinil having an instantaneous melting point of 153° - 154°C is Form I (-)-modafinil.

(23) The data reported herein shows that recrystallization from ethanol may lead to Form I (-)-modafinil but also produces other polymorphic forms. The data further shows that varying the conditions under which ethanol recrystallization is performed, such as the rate of cooling, the grade of ethanol utilized, the (-)-modafinil concentration, and the length of time the crystals are held at the final crystallization temperature prior to analysis produces different polymorphic forms, and one cannot predict that a specific polymorphic form will necessarily be produced by recrystallization of (-)-modafinil from ethanol without information regarding such variables. Since the Lafon '855 patent does not provide information on these conditions, I conclude that Form I (-)-modafinil is not the natural or necessary result flowing from the teaching or practice of the Lafon '855 patent.

(24) I have read and am familiar with U.S. 2004/0102523 A1 ("the Broquaire, et al. application"). This application describes several polymorphic forms of the modafinil racemate, along with their PXRD spectra. The Broquaire et al. application does not describe any polymorphic forms of (-)-modafinil, and none of the polymorphs described in Broquaire et al. exhibit the PXRD spectrum of the Form I (-)-modafinil polymorph that is the subject of the present application.

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7 In the interest of full disclosure, it is noted that I, and other scientists at Cephalon, Inc., have measured the melting point of samples of (-)-modafinil using means different from the Hofler hot bar device used to measure instantaneous melting points. These melting points were obtained on a different type of instrument, by a different method that involved progressively raising the temperature of a sample at a rate of 3-7°C/minute, and identifying the temperature range at which melting occurred. The results of these experiments are shown in Exhibit 5. The melting point obtained for samples of Form I (-)-modafinil ranged between 146.9 – 157 °C, while the melting point of Form II (-)-modafinil ranged between 146 – 149.6 °C. A mixture of Form I and Form II was found to have a melting point of 151.6 – 152 °C. These values are, in general, several degrees lower than the instantaneous melting points obtained with the Kofler hot bar. Accordingly, the absolute values obtained using different instrumentation cannot be directly compared. However, this data is internally consistent with Form I (-)-modafinil having a higher melting point range than other polymorphic forms of (-)-modafinil.

(25) I have also read and am familiar with WO 02/10125 ("the Singer, et al. reference"). This reference describes polymorphic forms of modafinil, but provides no disclosure of polymorphic forms of (-)-modafinil. Moreover none of the polymorphs described in Singer et al. produce a PXRD spectrum that corresponds to the PXRD spectrum of the Form I (-)-modafinil polymorph that is claimed in the present invention.

(26) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 7, 2006

John P. Mallamo

John P. Mallamo, Ph.D.

EXHIBIT 1

John P. Mallamo, Ph.D.

Home Address:
98 MacLeod Pond Road
Glenmoore, PA.
19343
(610) 458-9162

Work Address:
Cephalon, Inc.
145 BrandywinePkwy.
West Chester,PA 19380
(610)-738-6366

Education:

B.S. Chemistry, Colorado State University, Fort Collins, CO, 1977
Undergraduate Research Fellowships in Chemistry 1974-1977 (in the labs of A.I. Meyers and K.E. DeBruin)

Ph.D. Organic Chemistry, Johns Hopkins University, Baltimore, MD, 1981 (Biochemistry as Second)
E.M. Marks Award in Organic Chemistry, 1980
Thesis Advisor: Professor Gary H. Posner

Thesis Title: Part 1 - Sequential Carbon -Carbon Bond Formation: Cascade Annulations.
Part 2 - Asymmetric Induction during Conjugate Addition to Chiral a,b-Ethylenic Sulfoxides

Employment Positions Accepted:

September 1981, Sterling-Winthrop Research Institute
Medicinal Chemistry Department, Senior Research Chemist

January 1994, Cephalon Inc.
Director of Chemistry

Job Titles:

Sterling Drug, Inc. 9/81 – 12/93 (Sanofi-Winthrop)

1982 Assoc Project Chemist (Mentorship program) – Cardiovascular.
1983 Project Chemist - Antiviral Program (Discovered Phase 1 compound WIN54954)
1985 Group Leader, Medicinal Chemistry. Antivirals and Steroid receptor ligand projects.
1986 Project Chemist - Prostatic Diseases Program (Discovered Zanoterone®, 2 backups in development)
1987 Group Leader II - (Designed Danazol SBA – prodrug of existing product)
1989 Project Chemist - Neurodegeneration, Excitatory Amino Acid Antagonists.
1990 Principal Investigator
1991 Assistant Research Director, Medicinal Chemistry and Discovery KiloLab
1992 Therapeutic Area Co-Chair, Director Neuroscience Research (Discovered development candidate compound WIN63480)

Cephalon, Inc. 1/94 - present

1994 Director, Chemical Research - Cephalon, Inc.
1995 Senior Director, Medicinal Chemistry
1998 Vice President, Drug Discovery
1999 Vice President, Drug Discovery and Chemical Development
2002 Vice President, WW Chemical R&D

Current Responsibilities:
Lead a team of department directors with a mission to design and direct the synthesis, and evaluation of compounds with novel structure/activity - ensure the timely emergence and aggressive development of new chemical leads. Direct/lead the research and activities of the Departments of Medicinal Chemistry, Hit-to-Lead, Computational Chemistry and Chemical Development resulting in a regular/timely schedule of IND and NDA filings. Organizational responsibility for more than 65 chemists and engineers.

Coordinate worldwide activities in all aspects of organic chemistry as applied to the pharmaceutical industry. Coordinate all chemical process research activities providing efficient syntheses of key molecules. Ensure the timely synthesis of cGMP grade samples for development and clinical purposes through Phase 2. Leadership and line-management responsibilities for pilot plant operations in the US and France. Ensure appropriate process engineering enabling event-free Manufacturing Development. Interface with and serve on senior management teams several corporate collaborations and joint ventures. Ensure compliance with budgetary allocations.

Related Experience:

Antihypertensives (PDE inhibitors).
Antirheumatics, Antiinflammatories.
Antivirals (Picornavirus, Rhinovirus).
Antiandrogens (Prostatic Diseases).
Opiate and Non-Opiate Analgesics.
Antipsychotics (atypical).
Excitatory Amino Acid Antagonists.
Neurotrophic Molecules.
b-Amyloid Processing.
Antiproliferatives (Oncology).
Kinase Inhibitors.
Protease inhibitors.
Patent Law.
Computational Chemistry/Molecular Modeling.
Combinatorial Chemistry/Parallel Synthesis/Automated Chemistry

Special Training:

Performance Management, September 1992.
Managing Conflict, January 1992.
Key Manager Training, 1990-1992.
Completed Staffwork Workshop, January 1990.
Managing a Diverse Workforce, October 1989.
Frontline Leadership Program, 1988-1990 (a Kodak sponsored 3 year program).
Effective Presentations, March 1986.
Conducting Performance Appraisals, 1983, 1986, 1990, 1994, 1998.
Chemical Design Ltd.-Chemx Introductory and Advanced Courses.
Tripos Assoc. - Sybyl Intermediate and Advanced Courses, SPL Programming, Sybyl QSAR, ComFA.

Oral Presentations/Abstracts

R. Tripathy, J. Singh, E.R. Bacon, T.S Angeles, S.X. Yang, M.S. Albom, L. Aimone, J. Herman, C. Robinson, H. Chang, B.A. Ruggeri, C. Dionne, J. P. Mallamo, "1,2,3 Thiadiazole substituted Pyrazolones: Potent VEGFR2/KDR Kinase inhibitors." Presented at the 226th National ACS Meeting, NY, NY, September 7-11, 2003.

R. Tripathy, A. Reiboldt, P.A. Messina, G. Hostetler, R.M. Giuliano, > Iqbal, J. Singh, E. R. Bacon, T.S. Angeles, S.X. Yang, M.S. Albom, L. Aimone, C. Robinson, H. Chang, B.A. Ruggeri, C. Dionne, and J.P. Mallamo, Heterocyclic Substituted Pyrazolones. A potent class of VEGFR-2 kinase inhibitors. Presented at the 28th National Medicinal Chemistry Symposium, June 2002.

D. Gingrich, R. Hudkins, D. Reddy, J. Singh, B. Ruggeri, C. Robinson, H. Chang, K. Hunter, C. Dionne, and J. Mallamo Identification, SAR and Preclinical Development of a Novel Inhibitor of VEGF-dependent Angiogenisis. CEP-7055. Presented at the 223rd National ACS Meeting, Orlando Florida, April 2002. First Disclosure conference. Cited in C&E News

T. Underiner, M. Iqbal, J. Mallamo, D. Reddy, A. Reiboldt, J. Singh, and R. Tripathy, "C12, N13 Heterocyclic Bridiged Fused Pyrroloindenocarbazoles. Paper #622, 222nd ACS National Meeting, August 26-30, 2001.

J. Mallamo "New Inhibitors of rh-Calpain I", Presented at the First ITB Conference, Montreal, CN, April 18, 1999.

R. Hudkins, C. Murakata, M. Kaneko. T. Angeles, C. Dionne, N. Neff, J. Vaught, and J. Mallamo "Selective trk-A tyrosine kinase inhibitors", Presented at the 214th ACS Meeting, Dallas, Texas, April 1998.

G.J. Wells, R. Tripathy, J.P. Mallamo, R. Bihovsky, M.A. Ator, S. Mallya, S.E. Senadhi, D. Bozycko-Coyne, and R. Siman, "Dipeptidyl Benzotriazol-1-yl- and Benzotriazin-4-one-3-yl oxomethyl ketones as potent, highly selective inhibitors of Calpain I", presented at the 213th ACS Meeting Las Vegas, Nevada, September 1997.

J.P. Mallamo, et. al., "Neurotrophic Derivatives of K252a." presented at the 50th Anniversary Gordon Research Conference on Medicinal Chemistry. Colby-Sawyer College, NH, August 3-7, 1997.

Jani, J.P., Emerson, E., Camoratto, A.M., Hudkins, R.L., Mallamo, J.P., Murakata, C., Issacs, J., Skell, J., Neff, N., Vaught, J., and Dionne, C., "Evaluation of the antitumor efficacy of CEP-2563 for the treatment of prostate cancer." Proceedings of the American Association for Cancer Research (AACR) 88:3148 (1997)

J.P. Mallamo, "Novel and Selective Inhibitors of Calpain: Unexpected P2 Tolerance." Presented at the International Symposium on the Calpains: Role in Neurodegeneration, Oxford University, UK, April 12, 1997.

J.P. Mallamo, et. al., "Potent and Selective Neurotrophic Derivatives of K252a. SAR of Survival Promoting Analogs." Presented at the 211th National ACS Meeting, Orlando FL., August 23, 1996.

J.P. Mallamo, J.C. Kauer, R.L. Hudkins, D.P. Rotella, M.A. Glicksman, M. Saporito, S. Carswell, F. Haun, E. Knight Jr., N.T. Neff, J.L. Vaught, C. Murakata, M. Kaneko, "Potent and Selective Neurotrophic Derivatives of K252a." Presented at the Western Biotechnology Conference, San Diego CA, October 19, 1995.

J.P. Mallamo, J.C. Kauer, R.L. Hudkins, D.P. Rotella, M.A. Glicksman, M. Saporito, S. Carswell, F. Haun, E. Knight Jr., N.T. Neff, J.L. Vaught, C. Murakata, M. Kaneko, "Potent and Selective Neurotrophic Derivatives of K252a. Presented at the Second Symposium on Medicinal Chemistry Approaches to Alzheimer's Disease, Strasbourg, France, August 28, 1995.

R.L. Hudkins, J.P. Mallamo, J.C. Kauer, M.A. Glicksman, E. Knight Jr., N.T. Neff, J.L. Vaught, C. Murakata, M. Kaneko, "Structure-Activity Relationships of Neurotrophic Derivatives of K252a. Presented at the Second Symposium on Medicinal Chemistry Approaches to Alzheimer's Disease, Strasbourg, France, August 28, 1995.

M. Reuman, J.P. Mallamo, D.L. DeHaven-Hudkins, "Synthesis and Binding Affinity of 2,3,3a,4,9,9a-Hexahydro-9,4-(iminomethano)-1H-benz[f]indenes. Ligands for the PCP site of the NMDA Receptor." Presented at the Winter Conference on Medicinal and Bioorganic Chemistry, Steamboat Springs, CO., January 1995.

B. Ault, D. Luttinger, S.J. Ward, J.P. Mallamo, D. Martin, T.E. Salt, S.A. Eaton, X. Zheng, R.S. Zukin, M.S. Miller, "WIN 63480, A High Affinity Uncompetitive NMDA Channel Blocker, has Reduced Closed Channel Access Compared to MK-801" Presented at the Society for Neuroscience Meeting, Miami Beach, Florida, November 13-18, 1994.

Miller, M.S., Ault, B., DeHaven-Hudkins, D.L., Earley, W.G., Luttinger, D., Mallamo, J.P., and Ward, S.J. "WIN 63480: A Novel, Open Channel-Selective NMDA-Antagonist with Antiischemic Activity." Presented at the Society for Neuroscience Meeting, Miami Beach, Florida, November 13-18, 1994.

D.L. DeHaven-Hudkins, F.Y. Ford-Rice, J.D. Daubert, W. Earley, J.P. Mallamo, L.F. Lanyon, " Binding of the Novel Ligand [3H] WIN 63480 to the Phencyclidine (PCP) Receptor." Presented at The Society for Neuroscience Meeting, November 13-18, 1994.

T.R. Bailey, G.D. Diana, J.P. Mallamo, D. Cutcliffe, P.M. Carabateas, N. Vescio, R.C. Ogelsby, D.C. Pevear, "A Comparison of Antipicornaviral Activity between Selected 2-Acetylfurans and their Isoxazole Counterparts: Are 2-Acetylfurans Bioisosteres for 3-Methylisoxazoles?" presented at the National ACS Meeting, August, 1993.

Michael Reuman, J. Wetzel, and J.P. Mallamo, "On the Addition of Benzonitrileoxide to 1,1,1-Trifluoropropyne." presented at the Gordon Research Conference - Reactions & Procedures. 1993.

Guy D. Diana, D.M. Volkots, D. Cutcliffe, R.C. Ogelsby, T.R. Bailey, J.P. Mallamo, T.J. Nitz and D.C. Pevear, "The Evaluation of Tetrazole Analogues Related to WIN 54954 Against Picornaviruses" Presented at the Wellcome Symposium in Antiviral Therapy, December 6, 1992.

John P. Mallamo, and J.R. Wetzel, "Synthesis of the 6-Oxo, 8,9,10-trifluoro-1H-pyrimido[1,2-c]quinoline and the 6-Oxo, 8,9,10-trifluoro-6H-benzo[c]quinoline Ring Systems" Presented at the 204th ACS National Meeting, Washington, D.C., August 23-28, 1992.

John P. Mallamo, G.D. Diana, D.C. Pevear, and F.J. Dutko, "Comparison of the Compound Binding Sites on Human Rhinovirus Type 14 and 1A for Analogues of Disoxaril." Presented at The Fifth International Conference on Antiviral Research, Vancouver, B.C., March 1992.

John P. Mallamo, "Recent Developments in Steroidal Antiandrogens" Presented at Indiana University, Chemistry Department, October 21, 1991.

John P. Mallamo, P.J. Kowalczyk, M.R. Bell, G.M. Pilling, W.R. Wetzel, S. Daum, V. Kumar, R.G. Christiansen, F.H. Batzold, R.C. Winneker, and P.E. Juniewicz, "Synthesis and Quantum Mechanical Characterization of Novel Steroidal Androgen Receptor Antagonists." Presented at The Second Annual Joint Meeting of the French and American Chemical Societies, Captiva Island, Fl., January 8-13, 1991.

John P. Mallamo, M. R. Bell, R. G. Christiansen, S. Daum, V. Kumar, G. M. Pilling, J. R. Wetzel, F. H. Batzold, R. C. Winneker, P. E. Juniewicz, and B. W. Snyder, "Synthesis and Preclinical Activity of Novel Steroidal Androgen Receptor Antagonists: Potential Agents for the Treatment of Proliferative Prostatic Disease." Gordon Research Conference - Medicinal Chemistry, Colby-Sawyer College, New London, N.H., August 6-10, 1990.

Matthew Miller, J. Healey, T. Allen, L. Fleissner, J. Mallamo, and D. DeHaven-Hudkins, "Prevention of NMDA Neurotoxicity in Cultured Cortical Neurons by PCP Ligands: Dissociation From Sigma Affinity and Identification of Novel Structures." Presented at the 82nd Kodak Interplant Symposium, Rensselaer, N.Y., June 1990.

John P. Mallamo, F.H. Batzold, J.R. Wetzel, G.M. Pilling, S. Daum, V. Kumar, R.C. Winneker, and M.R. Bell, "Androgen Receptor Affinity of Heterocycle-Fused Androstanes: Electrostatic Complementarity of Some 5-Member Heterocycles." Presented at the 81st Kodak Interplant Symposium, Rochester, N.Y., May 1990.

M.R. Bell, R.G. Christiansen, J.P. Mallamo, F.H. Batzold, J.R. Reel, Richard C. Winneker, B.W. Snyder, and H.P. Schane, "Antiandrogenic Sulfonyl Pyrazoles." Presented at the Northeastern Regional Meeting of the American Chemical Society, June 1989.

Guy D. Diana, M.J. Otto, J.P. Mallamo, D. Cutcliffe, and M.A. McKinlay, "Synthesis and Structure-Activity Studies of Some Disubstituted Phenylisoxazoles Against Human Picornaviruses." Presented at the NERM Eastern Regional Meeting of the American Society, November 1987.

Guy D. Diana, M.J. Otto, J.P. Mallamo, D. Cutcliffe, and M.A. McKinlay, "Synthesis and Structure-Activity Studies of Some Disubstituted Phenylisoxazoles Against Human Picornaviruses." Presented at the NATO Conference, Milan, Italy, May 1987.

Publications:

Gingrich DE, Reddy DR, Iqbal MA, Singh J, Aimone LD, Angeles TS, Albom M, Yang S, Ator MA, Meyer SL, Robinson C, Ruggeri BA, Dionne CA, Vaught JL, Mallamo JP, Hudkins RL., A new class of potent vascular endothelial growth factor receptor tyrosine kinase inhibitors: structure-activity relationships for a series of 9-alkoxymethyl-12-(3-hydroxypropyl)indeno[2,1-a]pyrrolo[3,4-c]carbazole-5-ones and the identification of CEP-5214 and its dimethylglycine ester prodrug clinical candidate CEP-7055. J Med Chem. 2003 Dec 4;46(25):5375-88.

R. Bihovsky, M. Tao, J.P. Mallamo, G.J. Wells, "1,2-Benzothiazine 1,1-dioxide alpha-ketoamides analogues as potent calpain I inhibitors." Bioorganic & Medicinal Chemistry Letters 14, 2004 1035-1038.

Ruggeri B, Singh J, Gingrich D, Angeles T, Albom M, Chang H, Robinson C, Hunter K, Dobrzanski P, Jones-Bolin S, Aimone L, Klein-Szanto A, Herbert JM, Bono F, Schaeffer P, Casellas P, Bourie B, Pili R, Isaacs J, Ator M, Hudkins R, Vaught J, Mallamo J, Dionne C. "CEP-7055: a novel, orally active pan inhibitor of vascular endothelial growth factor receptor tyrosine kinases with potent antiangiogenic activity and antitumor efficacy in preclinical models." Cancer Res. 2003 Sep 15;63(18):5978-91.

D.R. Reddy, M.A. Iqbal, R.L. Hudkins, P.A. Messina-McLaughlin, and J.P. Mallamo, "A simple synthetic procedure for the protection of amides, lactams, ureas, and carbamates." , Tetrahedron Letters, 43, 2002, 8063-8066.

Ted L. Underiner, John P. Mallamo, and Jasbir Singh, "Syntheses of C12, N13 Heterocyclic Bridged Fused Indenopyrrolocarbazoles" , J. Organic Chemistry 67, 2002, 3235-3241.

Rabindranath Tripathy, Keith S. Learn, Dandu R. Reddy, Mohamed Iqbal, Jasbir Singh and John P. Mallamo, Construction of a kinase inhibitor library via parallel synthesis. Tetrahedron Letters 43, 2002, 217–220.

Kurt A. Josef, Frederick W. Kauer John Mallamo and Ron Bihovsky, Potent peptide α-Ketohydroxamate inhibitors of recombinant human calpain I. Bioorganic and Medicinal Chemistry Letters 2001, 11:19:2615-2617

Chikara Murakata, Masami Kaneko, George Gessner, Thelma S. Angeles, Mark A. Ator, Teresa M. O'Kane, Beth Ann W. McKenna, Beth Ann Thomas, Joanne R. Mathiasen, Michael S. Saporito, Donna Bozyczko-Coyne, John P. Mallamo & Robert L. Hudkins, Mixed lineage kinase activity of indolocarbazole analogues [Short Communication] Bioorganic and Medicinal Chemistry Letters Fast (2001)

Rabindranath Tripathy, Keith S. Learn, Dandu R. Reddy, Mohamed Iqbal, Jasbir Singh & John P. Mallamo
Construction of a kinase inhibitor library via parallel synthesis [Short Communication] Tetrahedron Letters Fast

Tripathy .R, Ator M.A., Mallamo J.P., "Calpain inhibitors based on the quiescent affinity label concept: high rates of calpain inactivation with leaving groups derived from N-hydroxy peptide coupling reagents. Bioorg. Med. Chem. Lett. 2000 Oct 16;10(20):2315-9.

S. Chatterjee. D. Dunn, M. Tao, G. Wells, Z. Gu, R. Bihovsky, M.A. Ator, R. Siman, and J.P. Mallamo, "P2-Achiral, P'-Extended alpha-ketoamide Inhibitors of Calpain I", Bioorganic and Medicinal Chemistry Letters 9, 2371-2374 (1999).

M. Tao, R. Bihovsky, G.J. Wells, and J.P. Mallamo, "Novel peptidyl phosphorus derivatives as inhibitors of human calpain I." J, Med. Chem. 41(20) 3912-3916 (1998).

R.L. Hudkins, M. Iqbal, C-H Park, J. Goldstein, J.L. Herman, E. Shek, C. Murakata, and J.P. Mallamo, "Prodrug Esters of the Indolocarbazole CEP-751 (KT-6587)" Bioorganic and Medicinal Chemistry Letters 8, 1873-1876 (1998).

S. Chatterjee, Z. Gu, D. Dunn, M. Tao, K. Josef, R. Tripathy, R. Bihovsky, S. Senadhi, T. O'Kane, B. McKenna, S. Mallya, M. Ator, D. Bozyczko-Coyne, R. Siman, J. Mallamo, "d-Amino Acid Containing High-Affinity Inhibitors of Recombinant Human Calpain I." J. Med. Chem. 41, 2663-2666 (1998).

S. Chatterjee, M. Iqbal, S. Mallya, S. Senadhi, T. O'Kane, B. McKenna, D. Bozcyko-Coyne, J. Kauer, R. Siman, and J. Mallamo, "Exploration of the importance of the P2-P3 -NHCO- moiety in a potent di- or tripeptide inhibitor of calpain I: Insights into the development of nonpeptide inhibitors." Bioorganic and Medicinal Chemistry 6, 1-14 (1998).

M. Kaneko, Y. Saito, H. Saito, T. Matsumoto, Y. Matsuda, J.L. Vaught, C.A. Dionne, T.S. Angeles, M.A. Glicksman, N.T. Neff, D.P. Rotella, J.C. Kauer, J.P. Mallamo, R.L. Hudkins, C. Murakata, "Neurotrophic 3,9-Bis[(alkylthio)methyl] - and -Bis(alkoxymethyl)-K252a Derivatives." J. Med. Chem. 40, 1863-1869 (1997).

S. Chatterjee, S. Senadhi, D. Bozyczko-Coyne, R. Siman, J.P. Mallamo, "Nonpeptidic Inhibitors of Recombinabt Human Calpain I." Bioorganic and Medicinal Chemistry Letters 7(3), 287-290 (1997).

S. Chatterjee, M. Iqbal, J.C. Kauer, J.P. Mallamo, S. Senadhi, S. Mallya, D. Bozyczko-Coyne, R. Siman, "Xanthene Derived Nonpeptidic Inhibitors of Recombinant Human Calpain I." Bioorganic and Medicinal Chemistry Letters 6(13), 1619-1622 (1996).

S. Chatterjee, K. Josef, G. Wells, M. Iqbal, R. Bihovsky, J.P. Mallamo, M.A. Ator, D. Bozyczko-Coyne, S. Mallya, S. Senadhi, R. Siman, "Potent Flouromethyl Ketone Inhibitors of Human Recombinant Human Calpain I." Bioorganic and Medicinal Chemistry Letters 6(11), 1237-1240 (1996).

Iqbal, M., Chatterjee, S., Kauer, J.C., Mallamo, J.P., Messina, P.A., Reiboldt, A., Siman, R., "Potent a-Ketocarbonyl and Boronic Ester Derived Inhibitors of the Proteosome." Bioorganic and Medicinal Chemistry Letters 6(3), 287-290 (1996).

C. Subramanyam, S. Chatterjee, J.P. Mallamo, "A Convenient Synthesis of 3-Substituted Pipecolic Acid Methyl Esters." Tetrahedron Lett., 37, 459 (1996).

B. Ault, M. Miller, M. Kelly, L. Hildebrand, W. Earley, D. Luttinger, J. Mallamo, J. Mallamo, S. Ward, "WIN 63480, A Hydrophillic TCP-site Ligand, has Reduced Agonist-independent NMDA Ion Chanel Access Compared to MK801 and Phencyclidine." Neuropharmacology, 34(12), 1597 (1995).

M. Reuman, J. Wetzel, J.P. Mallamo, "On the Addition of Benzonitrile Oxide to 3,3,3-Trifluoropropyne." Tetrahedron Letters (in preparation).

W.G. Earley, J.P. Mallamo, V. Kumar, C. Subramanyam, J.A. Dority Jr., M.S. Miller, D.L. DeHaven-Hudkins, L. Aimone, M. Kelly, B. Ault, "Novel Benzo[b]quinolizinium Cations as Uncompetitive NMDA Antagonists: The Relationship Between Log D and Closed vs Open Channel Block." J. Med. Chem. 38, 3586 (1995).

C. Subramanyam, J.P. Mallamo, G.M. Pilling, W.G. Earley, P.M. Carabateas, J.R. Wetzel, D.L. Dehaven-Hudkins, T. Allen, R.K. Kullnig, "Synthesis and Evaluation of 6,11-Ethanohexahydrobenzo[b]quinolizidines: A New Class of Noncompetitive N-Methyl-d-Aspartate Antagonists." J. Medicinal Chemistry, 38, 2483 (1995).

V. Kumar, P.M. Carabateas, J.A. Dority jr., W.G. Earley, J.P. Mallamo, C. Subramanyam, L. Aimone, B. Ault, D.L. DeHaven-Hudkins, M.S. Miller, "Novel NMDA Antagonists: Replacement of the Pyridinium Ring of 6,11-Ethano-benzo[b]-quinolizinium Cations with Heteroquinolinium Cations." J. Med. Chem. 38, 1826 (1995).

M. Reuman, J.P. Mallamo, D.L. DeHaven-Hudkins, "Synthesis and Binding Affinity of 2,3,3a,4,9,9a-Hexahydro-9,4-(iminomethano)-1H-benz[f]indenes. Ligands for the PCP site of the NMDA Receptor." Bioorganic and Medicinal Chemistry Letters 5(4) 371 (1995).

D.L. Dehaven-Hudkins, F.Y. Ford-Rice, J.D. Daubert, W.G. Earley, J.P. Mallamo, and L.F. Lanyon, "3[H]WIN 63480, A Novel Ligand for the Phencyclidine Recognition Site of the NMDA Receptor Complex." J. Neurochemistry xxx (1995).

P.M. Henrichs, L.L Musza, C.A. Rodger, E. Jaeger, W.G. Earley, J.P. Mallamo, V. Kumar, and C. Subramanyam, "An NMR Study of the Conformations of 12,12-Diaryl-6,11-ethano-Benzo[b]quinolizinium Compounds." J. Magnet. Resonance xxxx (1995).

C. Subramanyam, J.P. Mallamo, J.A. Dority Jr., W.G. Earley, V. Kumar, L.D. Aimone, B. Ault, M. MIller, D.A. Luttinger, and D.L. DeHaven-Hudkins, "Discovery of 6,11-Ethano-12,12-Diaryl-6,11-dihydrobenzo[b]quinolizinium Cations, a Novel Class of N-Methyl-D-aspartate Antagonists" J. Med Chem. 38, 21 (1995).

W.G. Earley, J.A Dority Jr., Virendra Kumar, and J.P. Mallamo, "Regiocontrolled Syntheses of Benzo[b]quinolizinium and Heteroisoquinolinium Cations." Heterocycles 41, 309 (1995).

J.P. Mallamo, W.G. Earley, V. Kumar, C. Subramanyam, J.A. Dority Jr., M.S. Miller, D.L. DeHaven-Hudkins, B. Ault, J.L. Hermann Jr., J-S Dung, L.A. McMullen, E. Jeager, R. Kullnig, L.J. Magee, "Identification, Synthesis, and Characterization of a Unique Class of NMDA Antagonists. The 6,11-Ethano-Benzo[b]quinolizinium Cation." J. Med. Chem. 37, 4438 (1994).

T.R. Bailey, G.D. Diana, J.P. Mallamo, N. Vesico, T.L. Draper, P.M. CArabateas, M.A. Long, V. Giranda, F.J. Dutko, D.C. Pevear, "An Evaluation of the Antirhinoviral Activity of Acylfuran Replacements for 3-Methylisoxazoles. Are 2-Acetylfurans Biosteres for 3-Methylisoxazoles?" J. Med. Chem. 37, 4177 (1994).

G.D. Diana, D. Cutcliffe, D.L. Volkots, J.P. Mallamo, T.R. Bailey, N. Vescio, R.C. Ogelsby, T.J. Nitz, J. Wetzel, V. Giranda, D.C. Pevear, F.J. Dutko, "Antipicornavirus Activity of Tetrazole Analogs of WIN 54954." J. Med. Chem., 36, 3240 (1993).

J.R. Wetzel and J.P. Mallamo, "Synthesis of the 6-Oxo-8,9,10-Trifluoro-1H-pyrimido[1,2-c]quinoline and the 6-Oxo-8,9,10-trifluoro-6H-benzo[c]quinoline Ring Systems." Tetrahedron Letters 1993.

G.D. Diana and J. P. Mallamo, "Correlation of Pocket Size and Shape with Antiviral Activity." J. Mol. Biol., 230, 206 (1993).

G.D. Diana, T.J. Nitz, J.P. Mallamo, and A.M. Treasurywala, "Antipicornavirus Compounds: Use of Rational Drug Design and Molecular Modeling." Antiviral Chemistry and Chemotherapy, 4(1), 1, (1993).

T.R. Bailey, G.D. Diana, P.J. Kowalczyk, M.A. Eissenstat, D. Cutcliffe, J.P. Mallamo, P.M. Carabateas and D.C. Pevear, "Antirhinoviral Activity of Heterocyclic Analogs of Win 54954." J. Med. Chem., 35, 4628, (1992).

J.P. Mallamo, G.D. Diana, D.C. Pevear, F.J. Dutko, M.S. Chapman, K.H. Kim, I. Minor, M. Olivera and M.G. Rossman, "Conformationally Restricted Analogues of Disoxaril: A Comparison of the Activity against Human Rhinovirus Types 14 and 1A." J. Med. Chem., 35, 4690, (1992).

J.R. Wetzel, J. Grego and John P. Mallamo, "An Improved Resolution of trans-2-Hydroxy-5,9-dimethyl-6,7-benzomorphans." CHIRALITY, 4, 439 (1992).

B.-C. Chung, J.P. Mallamo,P.E. Juniewicz and C.H.L. Shackleton, "Synthesis of deuterium labeled 5-alpha-androstane-3-alpha,17-beta-diol and its 17-beta-glucuronide." Steroids., 57, 530, (1992).

J.P. Mallamo, G.M. Pilling, W.R. Wetzel, M.R. Bell, P. Kowalczyk, H. Luss, R. Kullnig, F.H. Batzold, P. Juniewicz and R.C. Winneker, "Antiandrogenic Steroidal Sulfonyl Heterocycles. Utility of Electrostatic Complementarity in Defining Bioisosteric Sulfonyl Heterocycles." J. Med. Chem., 35, 1663, (1992).

R.G. Christiansen, M.R. Bell, T.E. D'Ambra, J.P. Mallamo, J.L. Herrmann, J.H. Ackerman, C.J. Opalka, R.K. Kullnig, R.C. Winneker, B.W. Snyder, F.H. Batzold, and P.H. Schane, "Antiandrogenic Steroidal Sulfonyl Pyrazoles." J. Med. Chem., 33, 2094 (1990).

J.P. Mallamo, "A New and Convenient Synthesis of Isobenzofurans: Tin II Chloride Mediated Cyclization of Benzene Dimethanols." TNTM, 3(2), 3 (1989).(a Kodak Publication)

J.P. Mallamo and P.E. Juniewicz, "New Horizons in the Treatment of Proliferative Prostatic Disease." Ann. Rep. Med. Chem., 24, 197 (1989).

G.D. Diana, D.Cutcliffe, R.C. Oglesby, M.J. Otto, J.P. Mallamo, V. Akullian, and M.A. McKinlay, "Synthesis and Structure-Activity Studies of Some Disubstituted Phenylisoxazoles against Human Picornavirus." J. Med. Chem., 32, 450-455 (1989).

G.D. Diana, R.C. Oglesby, V. Akullian, P.M. Carabateas, D. Cutcliffe, J.P. Mallamo, M.J. Otto, M.A. McKinlay, E.G. Maliski, and S.J. Michalec, "Structure-Activity Studies of 5-[[4-(4,5-dihydro-2-oxazolyl)-phenxoyl]alkyl]-3-methyl- isoxazoles: Inhibitors of Picornavirus Uncoating." J. Med. Chem., 30, 383 (1987).

J.P. Mallamo, M. Hulce, L.L. Frye, T.P. Kogan, G.H. Posner, "(S)-(+)-(p-Toluene Sulfinyl)-2-cyclopentanone: Precursor for Enantioselective Synthesis of 3-Substituted Cyclopentanones" Organic Synthesis, 64, 196 (1986).

G.H. Posner, J.P. Mallamo, K. Miura, M. Hulce, T.P. Kogan, "Asymmetric Synthesis Using Enantiomerically Pure Sulfoxides" Curr. Trends Org. Synth., Proc. Int. Conf.,4th, 1982, (Pub 1983), 177-80.

G.H. Posner, J.P. Mallamo, K. Miura, M. Hulce, "Asymmetric Carbon-Carbon Bond Formation Using Enantiomerically Pure Vinylic Sulfoxides" ACS Symp. Ser., 139-54 (1982).

G.H. Posner, J.P. Mallamo, M. Hulce, L.L. Frye, "Asymmetric Induction During Organometallic Conjugate Addition To Enantiomerically Pure 2-(arylsulfinyl)-2-cyclopentanones" J. Am. Chem. Soc., 104 (15), 4180-5 (1982).

G.H. Posner, M. Hulce, J.P. Mallamo, S.A. Drexler, J. Clardy, "Complete Asymmetric Induction in Synthesis of Enantiomerically Pure Steroid Intermediates of Natural Configuration" J. Org. Chem., 46 (25), 5244-6, (1981).

G.H. Posner, J.P. Mallamo, A.Y. Black, "Tandem Michael-Michael-ring Closure (MiMiRc) Reactions. One Pot Steroid Total Synthesis. 9,11-Dehydroestrone." Tetrahedron, 37 (23), 3921-6, (1981).

G.H. Posner, J.P. Mallamo, K. Miura, "Asymmetric Induction During Organometallic b-Addition to a-Carbonyl, a,b-Ethylenic Sulfoxides." J. Amer. Chem. Soc. 103, 2886 (1981).

G.H. Posner, P. Tang, J.P. Mallamo, "Generation and Reactions of 1-(arylsulfinyl)alkenyllithium Reagents. Terminal Allenes From 2-alkenyl Aryl Sulfoxides." Tetrahedron Lett. 42, 3995-8, (1978).

Patents and Applications: (Foreign equivalents/applications of U.S. Patents not listed)

U.S. Patent # 5,053,405 :	Antiandrogenic Sulfonlysteroidothiazoles.
U.S. Patent # 5,068,234 :	3-arylcarbonly-1-(C-attached-N-ereroaryl)-1H-Indoles
U.S. Patent # 5,134,135 :	Antiandrogenic Sulfonylsteroidooxazoles.
U.S. Patent # 5,239,110 :	Phenylcyclohexanol derivatives as agents for treating CNS disorders.
U.S. Patent # 5,240,935 :	Substituted 2-azabicyclo[2.2.2]octane derivatives and compositions and method of use thereof
U.S. Patent # 5,286,733 :	Substituted 3-piperidinealkanoates and alkanones and compositions and method of use thereof
U.S. Patent # 5,290,789 :	Penta and tetrasubstituted piperidines and compositions and method of treating psychosis
U.S. Patent # 5,290,796 :	Substituted 3-piperidinealkanamines and alkanamides and compositions and method of use thereof
U.S. Patent # 5,324,737 :	3-Arylcarbonyl-1-(C-attached-N-heteryl)-1H-Indoles.
U.S. Patent # 5,364,867 :	4-phenylpiperdine agents for treating CNS disorders
U.S. Patent # 5,380,729 :	12-Hetero Substituted 6,11-Ethano-6,11-Dihydrobenzo[b]quinolizinium Salts and Compositions and Method of use thereof.
U.S. Patent # 5,430,036 :	6,11-substituted-6,11-dihydrobenzo[b]quinolizinium salts and compositions and method of use thereof.
U.S. Patent # 5,434,159 :	6,11-cyclyl-1,2,3,4,5,6,11,11a-octahydrobenzo[b]quinolines and compositions and method of use thereof.
U.S. Patent # 5,455,248 :	Substituted 6,11-Ethano-6,11-Dihydrobenzo[b]quinolizinium Salts and Compositions and Method of use thereof.
U.S. Patent # 5,498,616 :	Cysteine Protease and Serine Protease Inhibitors.
U.S. Patent # 5,554,620 :	Substituted 6,11-ethano-6,11-dihydrobenzo[b]quinolizinium salts and compositions and methods of use thereof.
U.S. Patent # 5,569,655 :	Substituted Heterocyclylisoquinolinium Salts and Compositions and Methods of use Thereof.
U.S. Patent # 5,604,224 :	Substituted heterocyclylisoquinolinium salts and compositions and methods of use thereof.
U.S. Patent # 5,631,264 :	Substituted 6,11-Ethano-6,11-dihydrobenzo[b]quinolizinium salts and compositions and methods of use thereof.
U.S. Patent # 5,639,732 :	Phosphorous-Containing Cysteine and Serine Protease Inhibitors.
U.S. Patent # 5,650,407 :	Selected Soluble Esters of Hydroxyl-Containing Indolocarbazoles.
U.S. Patent # 5,658,906 :	Cysteine and Serine Protease Inhibitors.
U.S. Patent # 5,686,444 :	Selected Soluble Esters of Hydroxyl-Containing Indolocarbazoles.
U.S. Patent # 5,736,696 :	Selected Derivatives of K252a.
U.S. Patent # 5,817,651 :	3-Arylcarbonyl-1-(C-Attached-N-Hereryl-1H-Indoles.
U.S. Patent # 6,083,944 :	Quinoline-containing alpha ketoamide cysteine and serine protease inhibitors.
U.S. Patent # 6,096,778 :	Alpha ketoamide multicatalytic protease inhibitors.
U.S. Patent # 6,100,267 :	Quinoline and naphthalenecarboxamides, pharmaceutical compositions and methods of inhibiting calpain.
U.S. Patent # 6,127,401 :	Bridged indenopyrrolocarbazoles.
U.S. Patent # 6,150,378 :	Peptidyl-containing alpha-ketoamide cysteine and serine protease inhibitors.
U.S. Patent # 6,288,231 :	peptidyl-containing alpha-ketoamide cysteine and serine protease inhibitors.
U.S. Patent # 6,306,849 :	Selected Derivatives of K252a.
U.S. Patent # 6,310,057 :	alpha-ketoamide Multicatalytic Protease Inhibitors.
U.S. Patent # 6,359.130 :	Bridged Indenopyrrolocarbazoles.
U.S. Patent # 6,492,396 :	Substituted thioacetamides.
U.S. Patent # 6,670,358 :	Substituted thioacetamides
U.S. Patent # 6,686,335 :	Hydroxamate-containing cysteine and Serine Protease inhibitors.
U.S. Patent # 6,703,368 :	Peptide-containing a-ketoamide Cysteine and Serine Protease Inhibitors.
U.S. Patent # 6,875,865 :	Selected derivatives of K252a.
U.S. Patent # 6,919,367 :	Substituted thioacetamides.

Computer Literacy:
SYBYL, AMPAC/MOPAC, Gaussian Series, MDL Software (MACCS, REACCS, ISIS), VAX-VMS, Oracle-SQL, Macintosh OS, MS-DOS, Windows, some UNIX and vBASIC. Advanced understanding of computational sciences as applied to drug discovery and development.

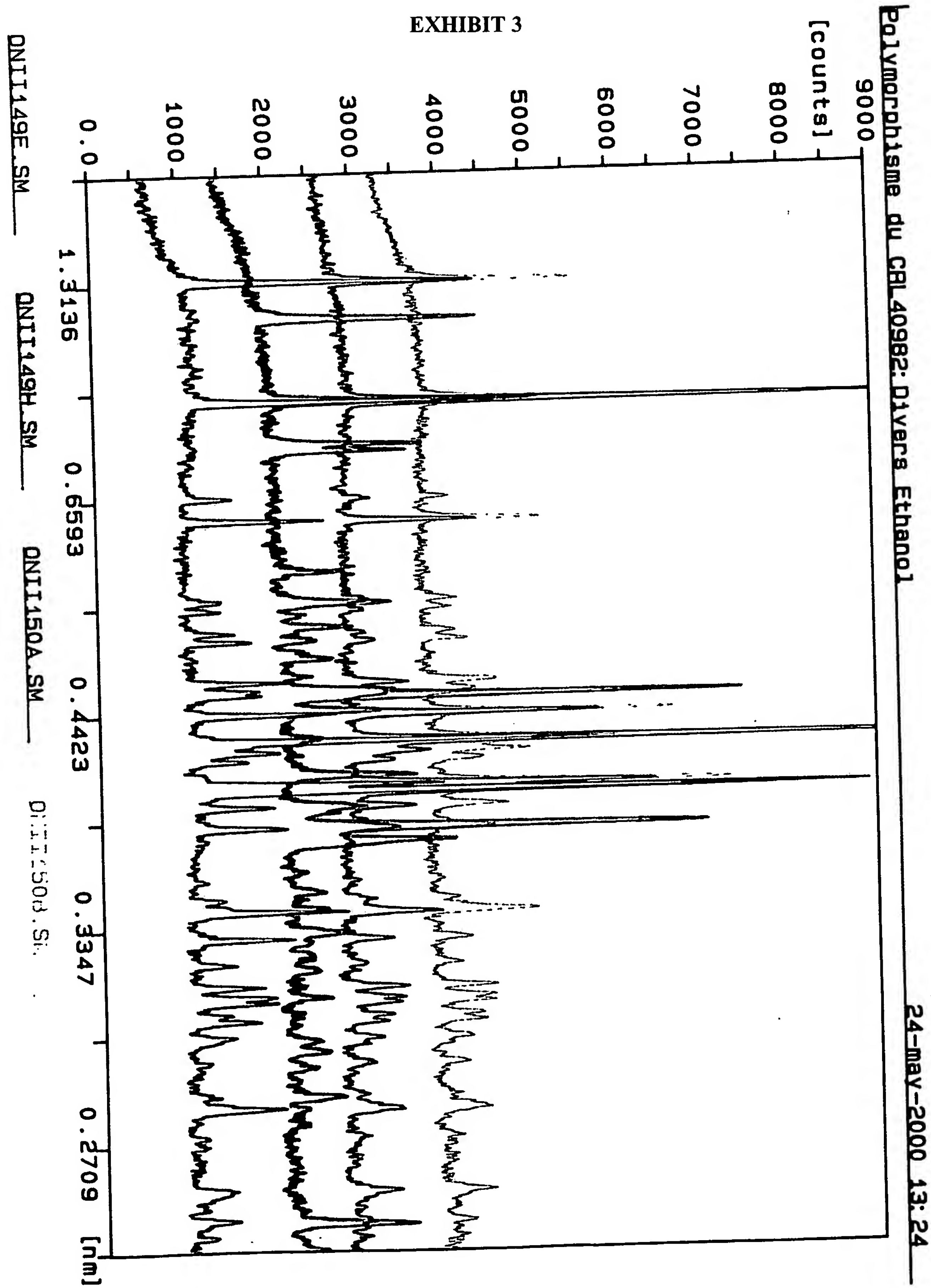
Professional Affiliations:
American Chemical Society, Organic and Medicinal Chemistry Divisions.
Program Committee, National Medicinal Chemistry Symposia : ACS, 1994-96.
American Association for the Advancement of Science.
Northeastern Division - ACS.
Reviewer for: J. Med. Chem., J. Org. Chem., Bioorganic Med Chem Letters, Tetrahedron Letters, Tetrahedron Asymmetry, Medicinal Chemistry.
Editorial Board, IDdb Patent Alerts - Neuroscience (1995- present). Current Drugs.
Science Advisory Board, IDdb Publications 1995 – present
Session Chair and Organizer, 1997 Gordon Research Conference (Med. Chem.) - Neurotrophic Molecules.
Session Chair and Organizer 2000 Gordon Research Conference (Med. Chem) – Poster Session
Session Chair and Organizer, 3rd Med Chem. Conference on Neurodegenerative Diseases. 1998
Conference Organizer, 4th International Med. Chem Conference on Neurodegenerative Diseases (February 2000).
Poster Session Chairperson – 2001 Medicinal Chemistry Gordon Conference
Board of Directors, Medicinal Chemistry of Neurodegenerative Diseases Foundation 1996-present
Board of Technical Directors, Nanotechnology Institute – Ben Franklin Technology partners
Nominated to Board of Directors, Synexis, Inc. (declined due to conflict of interest). 2002

EXHIBIT 2

Example No.	Recrystallization Procedure	Form Obtained
5/2502	(-)-modafinil was synthesized by ammonolysis of methyl (-) benzhydrylsulfinylacetate in MeOH and water. 100 g of the crude product was taken up in 500 ml absolute EtOH, heated to reflux, filtered, allowed to come to room temperature, then cooled in an ice bath. Crystals were filtered and dried. Yield 77 g. M.P. (inst.)= 153-154°C. These crystals were then dissolved in 500 ml absolute ethanol, heated to reflux, then left to cool to room temperature, with stirring. The crystals were filtered and dried. M.P. (inst.)= 163-164°C. PXRD analysis performed about 1 month later with a PW1840(Cu) diffractometer.	Form I
1/0054(a)	Crystals of (-)-modafinil were obtained by the same double recrystallization procedure set forth for Example 5/2502, on a larger scale. 163.5 g of product was obtained. M.P. (inst.)= 164°C. PXRD analysis performed about 9 months later with a PW1840(Cu) diffractometer.	Form I/ Form IV mixture
1/0054(b)	Sample of Example No. 1/0054(a) (*supra*) taken from storage re-analyzed by PXRD 5 years later with a PW1840(Cr) diffractometer.	Form I
1/0920	(-)-modafinil was synthesized by ammonolysis of methyl (-) benzhydrylsulfinylacetate in MeOH and water. 365.8 g of crude product was taken up in 1.83 L of denatured EtOH (w/2.5% toluene) and heated to 75°C to dissolve, then allowed to crystallize. 162 g of these crystals were taken up in 810 ml denatured EtOH (w/2.5% toluene), and heated to reflux. Solution was allowed to cool on bench top for 10 minutes, then transferred to an ice bath. Crystals were filtered and dried under vacuum at 30°C. M.P. (inst.)= 163°C PXRD analysis performed 10 days later with a PW1840(Cr) diffractometer.	Form I

ON II/149 E	Step a: (-)-modafinil was synthesized by ammonolysis of methyl (-) benzhydrylsulfinylacetate in MeOH and water. 66 g of crude product was taken up in 330 ml absolute EtOH, heated to reflux, filtered, and the hot filtrate immediately cooled in an ice bath. Crystals were filtered and dried under vacuum at 35°C. Yield 57 g. Step b: 7.85 g of product from Step a was mixed with 115 ml absolute EtOH and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. M.P. (inst.)= 162°C. PXRD analysis with a PW1840(Cr) diffractometer.	Form I
ON II/149 H	5 g of product from II/149 E Step a, was mixed with 80 ml denatured EtOH (w/2.5% toluene) and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. M.P. (inst.)= 156°C. PXRD analysis with a PW1840(Cr) diffractometer.	Form II
ON II/150 A	Step a: product from II/149 E Step a, was dissolved in a mixture of acetone, ethyl acetate, methanol, isopropanol, absolute ethanol, and propanol. The solvents were evaporated under vacuum using a rotator. The residue was dissolved in absolute ethanol, cooled to 20 °C, then placed in an ice bath. Crystals were filtered and dried in an oven. Step b: About 5 g of the product from II/150 A, Step a, was mixed with 70 ml denatured EtOH(w/2.5% toluene) + 3% H_2O and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. PXRD analysis with a PW1840(Cr) diffractometer.	Form I
ON II/150 B	About 5 g of the product from II/150 A, Step a, was mixed with 70 ml absolute EtOH + 3% H_2O and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. PXRD analysis with a PW1840(Cr) diffractometer.	Form I

EXHIBIT 3


Polymorphisme du CRL 40982: Divers Ethanol
24-may-2000 13:24
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7000
6000
5000
4000
3000
2000
1000
0.0
1.3136
0.6593
0.4423
0.3347
0.2709
[nm]
ONII149E.SM
ONII149H.SM
ONII150A.SM

Exhibit 4

Polymorphic Form Tested	Instantaneous Melting Point (°C)
Form I	163-164
Form I/Form IV mixture	164
Form I	163
Form I/Form IV mixture	161
Form I/Form II mixture	160
Form I	159
Form I/Form II mixture	156
Form I	162
Form I/Form II mixture	156
Form I	162
Form II	156
Form I	160

Exhibit 5

Polymorphic Form Tested (Blind)	Non-instantaneous Melting Point (°C)
Form I	154-156.2
Form I	155-156
Form I	156-157
Form I	153.7-154.9
Form I	149.7-150.6
Form I/Form II mixture	151.6-152
Form II	146-147.2
Form II	146.5-149.6
Form I	146.9-148.1